The New England
Journal of Medicine

Copyright, 1940, by the Massachusetts Medical Society

VOLUME 223 OCTOBER 17, 1940 NUMBER 16

THE PREVENTION OF DIABETES*

REGINALD E. HAIST, M.D.,† JAMES CAMPBELL, PH.D.,‡ AND CHARLES H. BEST, M.D.§

TORONTO, CANADA

WE have been emboldened by the results of our recent experiments, considered in relation to the work of Allen, Evans, Houssay, Young and others, to write an article under this provocative title. Although many years may be required to complete the obvious extensions of the present experiments, sufficient information is now available to show that the production of diabetes in experimental animals by the administration of pituitary diabetogenic substances may be prevented by dietary means or by the administration of large doses of insulin. Our studies have been concerned largely with the factors which affect the insulin content of the pancreas, and these findings support and extend those of previous workers, who have approached the same problem from other directions. The prevention of the diabetic condition by certain procedures makes it imperative that their curative effect also be thoroughly investigated.

PARTIAL PANCREATECTOMY

Minkowski, Hédon and others have shown that a very large portion of the pancreas must be removed before the diabetic condition appears. The beta cells of the islets of the pancreatic remnants in diabetic animals were shown by Homans[1] and Allen[2] to exhibit progressive degranulation and finally hydropic degeneration. Allen[3] claimed that in the early stages of hydropic degeneration certain procedures permitted recovery of the islets, whereas after the condition had been present for a sufficient length of time the degenerated cells failed to recover and gradually disappeared. Fasting restored the damaged tissue to a normal condition, if the diabetic state had not been present too long. Copp and Barclay[4] found that the administration of insulin tended to promote recovery in islets showing the hydropic degenerative changes resulting from extensive partial pancreatectomy. They concluded also that there was a significant reduction in the insulin requirements

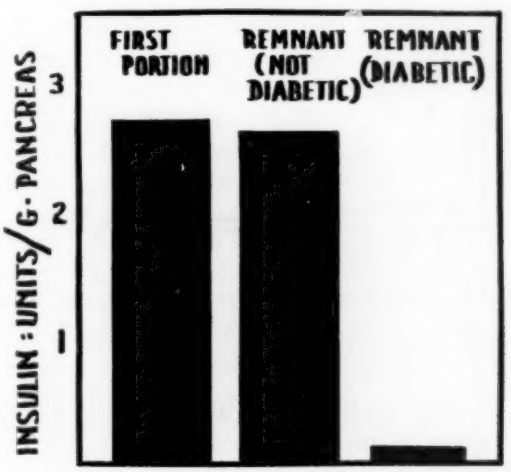


FIGURE 1. *Insulin Content of the Pancreas in Dogs Following Partial Pancreatectomy.*

as the islet cells recovered granulation. These observations were confirmed and extended by Bowie.[5] The results of the histological investigations, although not absolutely definite, strengthened the view that hydropic degeneration is the result of overstrain, and led to the conclusion that fasting or insulin administration tends to prevent it.

The conclusion that partial pancreatectomy increases the demands made on the remnant of pancreas is supported by the results of insulin assays (Haist and Best[6]). In partially depancreatized animals which had sufficient pancreas left to prevent the onset of diabetes, the insulin content per gram of the remnant of pancreas did not fall,

*From the Department of Physiology and the Department of Physiological Hygiene, University of Toronto.

Some of this material was presented by one of us (C. H. B.) as the Hughlings Jackson Memorial Lecture at the Montreal Neurological Institute on April 3, 1940, and as a lecture before the Boylston Medical Society, Harvard Medical School, on May 13, 1940.

†Assistant professor of physiological hygiene, University of Toronto.

‡Research associate, Department of Physiology, University of Toronto.

§Professor of physiology, University of Toronto.

even though the amount of tissue remaining was very small. If, however, enough pancreas was removed to render the animal diabetic, the insulin concentration in the remnant was reduced to a very low value (Fig. 1).

Since diabetes was not evident in many dogs from which a large part of the pancreas had been removed, it would seem logical to assume that the total amount of insulin liberated had not been greatly decreased; and since the insulin content of

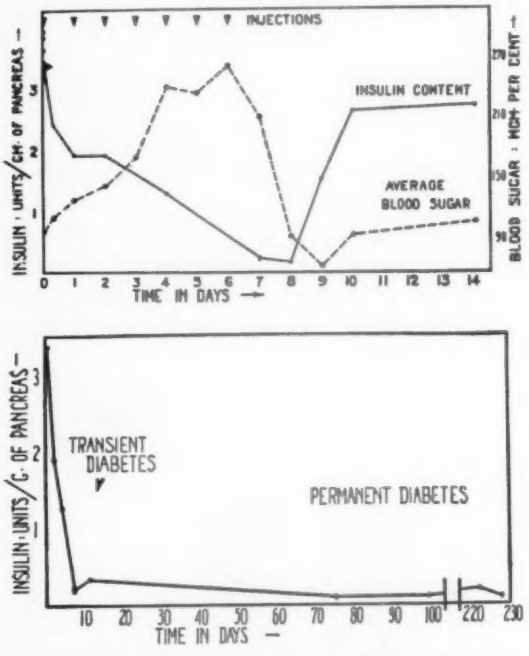


FIGURE 2. *The Effect of Anterior-Pituitary Extract on the Insulin Content of the Pancreas and on the Blood-Sugar Level in Dogs.*

the remnant did not fall, it would appear that the production of insulin was able to keep pace with its liberation. If these assumptions should prove to be correct, the production and liberation of insulin by the remnant over a given period must have increased. When the amount of tissue removed was still greater, the production of physiologically active insulin apparently was no longer able to keep pace with the liberation, and the insulin concentration in the remnant decreased. It therefore seems logical to consider that extensive partial pancreatectomy leads to hydropic degeneration of the islets and to reduction in the insulin content of the pancreas through overwork resulting from excessive demands on this organ for its internal secretion.

DIABETES INDUCED BY PITUITARY EXTRACTS

A condition of the pancreas similar to that found in the partially depancreatized animal is observed in dogs receiving daily injections of anterior-pituitary extract (Richardson and Young[7]). Under these circumstances there is a gradual fall in the insulin content of the pancreas to very low levels (Best, Campbell and Haist[8]) (Fig. 2). At the same time there is a progressive degranulation of the beta cells of the islets, followed by hydropic degeneration (Richardson and Young[7]; Ham and Haist[9]). Here too the islet cells may recover on cessation of the injections and the insulin content may return to a normal value, if the degenerative condition has not been present for too long a period. The changes in insulin content and in the appearance of the islet cells are similar to those observed in partially depancreatized animals and are probably due to the same cause, namely, overwork. The chief difference is that in the condition produced by the anterior-pituitary extract the whole pancreas, rather than a remnant, is involved. In the condition resulting from partial pancreatectomy the reduction in the amount of functioning tissue seems to be the most important factor, whereas in the condition caused by the administration of the extract the increase in the need for endogenous insulin probably plays a major role. There is as yet no evidence to support the possibility that in

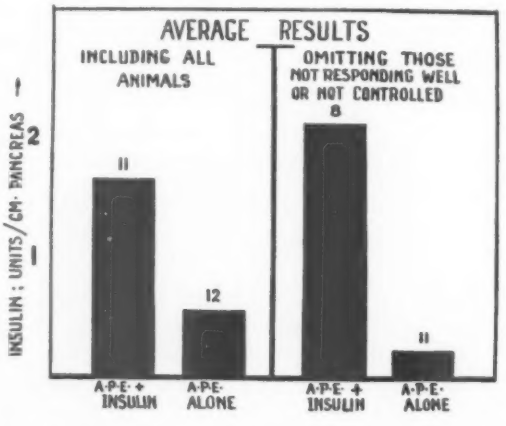


FIGURE 3. *The Effect of Anterior-Pituitary Extract and Insulin and of Anterior-Pituitary Extract Alone on the Insulin Content of the Pancreas in Dogs.*

the latter condition a reduction in the amount of functioning islet tissue results from a primary degenerative effect of the extract exerted directly on islet cells. There is evidence, however, that the need for insulin in these animals is increased. It has been shown (Houssay, Biasotti and Rietti[10]) that anterior-pituitary extract exerts its hyperglycemic and glycosuric effects in the absence of the pancreas, and that the injections of the extract antagonize the action of insulin even though the blood-sugar level is not elevated (Houssay and

Potick[11]; di Benedetto[12]; Cope and Marks[13]). These observations indicate that the extract has profound extrapancreatic effects so long as administration is continued. Evidence of cellular proliferation and cytoplasmic changes in many organs other than the pancreas in animals injected with the extract is further proof of this influence (Ham and Haist[9]). It is reasonable to suppose that the need for endogenous insulin is increased by the extrapancreatic effects. This hypothesis is further substantiated by the finding that insulin administration tends to prevent the fall in insulin content and the degenerative changes resulting from the injections of anterior-pituitary extract (Campbell, Haist, Ham and Best[14]) (Fig. 3).

Factors Influencing the Effects of Anterior-Pituitary Extract

In the previous section it was pointed out that insulin administration tends to prevent the degenerative effects and the lowering of the insulin content of the pancreas resulting from the administration of anterior-pituitary extract. Certain dietary factors also have a potent influence on the action of the extract. Houssay[15] has reported that the hyperglycemic effect of the anterior-pituitary extract is not obtained in fasting dogs. We have recently confirmed this finding and have noted that the feeding of fat has a similar effect. Our experiments show too that fasting or fat-feeding tends to prevent the rapid fall in the insulin content of the pancreas and the degenerative changes in the islet cells resulting from the daily administration of anterior-pituitary extract. All the injected animals in our series were previously tested for their sensitivity to the extract. The various groups had the same average initial sensitivity. Average values for the insulin content of the pancreases of the three dogs in each group are shown in Table 1. It is evident from these figures that fasting or fat feeding tends to prevent the rapid fall in the insulin content of the pancreas resulting from the daily injection of anterior-pituitary extract.*

Table 1. *The Effect of Anterior-Pituitary Extract on the Average Insulin Content of the Pancreas in Dogs on Various Diets.*

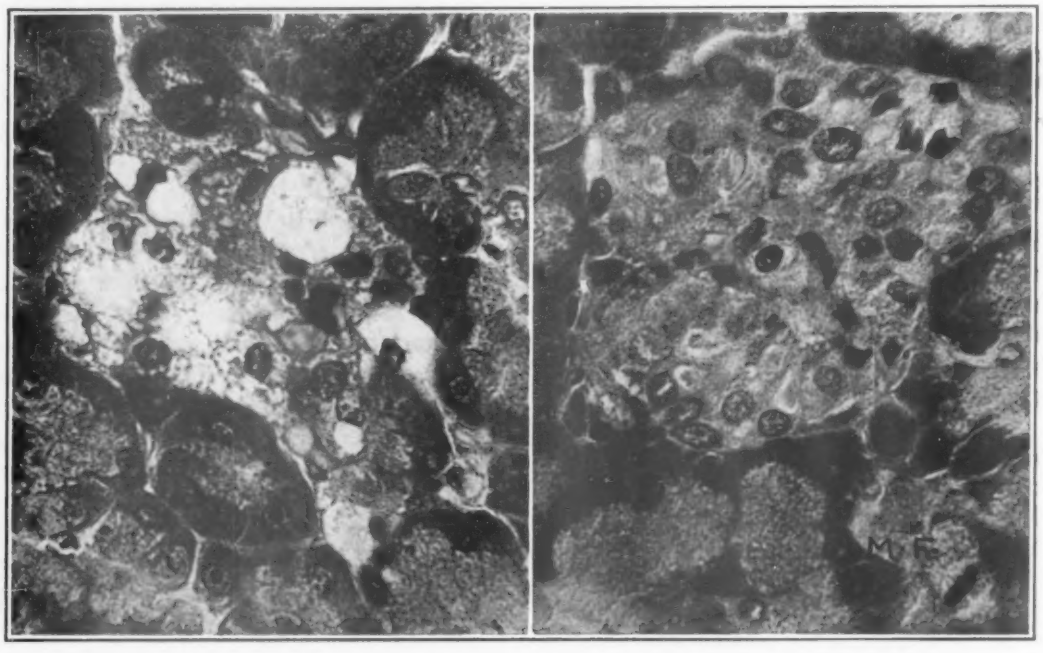
Experimental Group	Insulin Content of Pancreas *units/gm.*
Normal diet plus anterior-pituitary extract (7 days) — same caloric intake as fat group	0.5
Fat plus anterior-pituitary extract (7 days)	1.7
Fasted plus anterior-pituitary extract (7 days)	2.8
Fat-fed (18 days)	2.5
Fasted (9 days)	2.6
Normal diet (9 dogs)	3.2

The changes that occur during the administration of anterior-pituitary extract may be ascribed to the call on the pancreas for insulin, and may be prevented by lessening this demand. In the dog, the insulin content of the pancreas will return to normal and the islet cells will recover on cessation of the injections, provided the period of administration has not been too prolonged. If the injections are continued for sufficiently long periods and then stopped, the insulin content of the pancreas may remain permanently low and there is no recovery of islet cells. The beta cells degenerate and few if any are seen. Those that are present show a loss of granules. The permanent diabetic state probably results in large part from changes in the islet cells. In the transient type of diabetes observed while the extract is being administered, the islet-cell changes may be the result of the extrapancreatic effect, whereas in the condition of permanent diabetes which is present after the extract is discontinued, these changes, now permanent, are presumably responsible for the diabetes. The persistence of the condition therefore depends on the permanence of the change in the beta cells. If any procedure could cause recovery of the cells or lead to the formation of new ones, the condition would be cured. Fasting or fat-feeding (Young[16]; Marks and Young[17]; Dohan and Lukens[18]) relieves the diabetes in these animals, but as yet no conclusive proof has been given that such procedures restore the islet cells in the dog. Lukens and Dohan[19] find that in the partially depancreatized cat made permanently diabetic by injections of anterior-pituitary extract, the administration of insulin leads to a recovery of the islet cells and cure of the diabetic state. As yet, no one has demonstrated that restoration of islet cells or the formation of new ones can occur in the permanently diabetic dog.

The islet and acinar cells of the pancreas are thought to have their origin in the cells of the duct epithelium. This is true in the embryo and under certain conditions in the adult organism. Allen[3] found numerous vacuoles in the epithelium of the small ducts in partially depancreatized diabetic dogs. He suggested that the duct changes observed in these animals might represent an ex-

*The results on two other dogs are particularly interesting in this connection. One animal received a normal diet; the other had available only fat. While the second ingested moderately large amounts of fat during the first ten days, very small quantities were consumed during the latter part of the experiment. Both animals received daily injections of anterior-pituitary extract for thirty days. The animal on the normal diet became permanently diabetic; the other showed no signs of diabetes when after the thirty days a normal diet was gradually restored. The animals are still under observation.

haustion of a proliferative rather than an endocrine activity. Similar vacuoles in the small ducts of the pancreas have been noted in animals showing the temporary diabetes and those showing the permanent diabetes resulting from the injection of anterior-pituitary extract (Richardson and Young[7]; Richardson[20]; Ham and Haist[9]). This may be significant in connection with the failure of the islets to recover. The hope still remains, however, that proliferation without degeneration may lead to an increase in the islet tissue and a restoration of function in these animals. An increase in the islet tissue of normal animals as a result of the administration of anterior-pituitary extract has been noted by Anselmino, Herold and Hoffmann[21] and, with a different extract, by Richardson and Young.[22] In dogs treated with diabetogenic anterior-pituitary extract, proliferative changes were noted in the islets (Richardson and Young[7]) and also in the acini and ducts of the pancreas (Ham and Haist[9]). The finding of mitoses in ducts, acini and islets suggests that the mother cells of the ducts may be stimulated to differentiate into islet and acinar cells under the influence of the extract. It is important to note that the administration of insulin simultaneously with that of anterior-pituitary extract did not stop the proliferative changes, although the degenerative effects were, in large part, prevented (Campbell, Haist, Ham and Best[14]) (Fig. 4). The hope is raised that proliferation without degeneration, produced by the administration of anterior-pituitary extract along with adequate amounts of insulin, may lead to an increase in the islet tissue and a more nearly normal islet function.* The same effect might be achieved by a pituitary principle causing only proliferation of the islet cells, the presence of which is suggested by the recent work of Marks and Young.[23]



A B

FIGURE 4. *Histological Pancreatic Changes in Dogs.*

A *shows hydropic changes in the islet, the dog having received anterior-pituitary extract alone.*

B *represents the islet in a dog that received anterior-pituitary extract and insulin. Note the mitotic figure in the acinus in the lower right-hand corner.*

We may summarize the points discussed thus far by stating that when a large portion of the pancreas is removed from dogs, the islets of the remnant become exhausted, probably through overfunction. In this case the overwork results from the fact that less pancreas is available. When the extract of anterior pituitary gland is given, the whole pancreas becomes exhausted, and the

*In this connection the results of a recent preliminary experiment by one of us (J. C.) are of interest. Two dogs which had exhibited intense diabetes for some fifty days after the cessation of injection of anterior-pituitary extract were given a second series of injections of the extract for ten days. While receiving this treatment the animals were fasted and received very large injections of insulin at frequent intervals. They were then returned to exactly the same diet that they had previously received. The carbohydrate tolerance of one animal was only slightly changed, but a very dramatic improvement was found in the other. The permanence of this increased tolerance and the relative importance of the various factors involved in its production are as yet undetermined. It is obvious that the results of further experiments, in which histological and chemical studies on the pancreas before and after the "treatment" are included, will be most valuable.

overactivity probably results from the increased need for insulin, although a direct stimulation of the islets may play some part. When the islet changes become permanent and the injections are discontinued, the diabetes persists, because there is an inadequate number of functioning beta cells. The diabetic condition brought on by overstrain may be prevented or ameliorated by fasting, the feeding of fat or the administration of insulin. The fact that these procedures tend to reduce the activity of the islet cells is also indicated by some recent results that we have obtained.

Effect of Diet on the Insulin Content of the Pancreas

Fasting or feeding a diet of fat will lead to a definite reduction in the insulin content of the

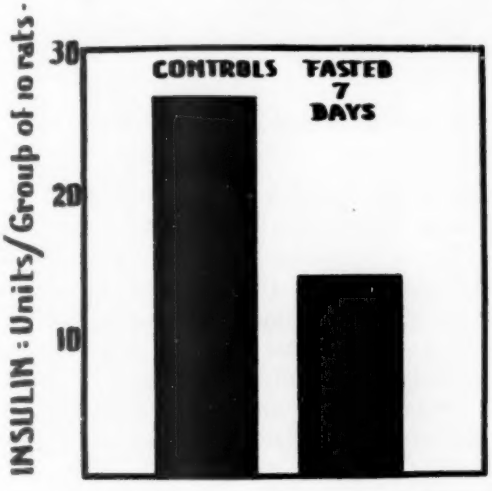


Figure 5. *Total Insulin Units in the Pancreases of Normal and Fasted Rats.*

pancreas of rats (Haist, Ridout and Best[24]; Best, Haist and Ridout[25]) (Figs. 5 and 6). Feeding a diet of sugar tends to prevent the fall in insulin content. When animals are paired and one group is fed with sugar and the other with fat to secure an equal caloric intake, at the end of fourteen days the insulin content of the pancreas in the sugar-fed group is much higher than that in the group receiving fat. The difference amounts to 42 per cent of the higher value. There is a moderate fall in the insulin content in the sugar-fed group. This is probably due to a reduced caloric intake, since male rats fed an inadequate amount of a balanced diet show a decrease in the insulin content of pancreas. The pancreases of the fasted or fat-fed rats do not show any marked degenerative change in sections stained with hematoxylin and eosin (Fig. 7), but granule studies have not yet been made.

In dogs, the effects of fasting or feeding of fat on the insulin content of the pancreas are not so readily demonstrable as they are in rats. This is probably due to variations in age, previous history and so forth when dogs are used, and to the smaller number of animals employed. Also, the effective fasting period for the dog is much longer than that for the rat. The average insulin values for several fasting and fat-fed dogs treated for the times noted are given in Table 1. The individual values were all in the lower part of the normal range, but a much larger series than the present is necessary in order to demonstrate the effects of fasting or fat-feeding alone in this species.

When various diets are given to rats fasted for seven days it is found that a balanced diet results in the return of the insulin content of the pancreas to normal; a diet of sugar restores the content to within the normal range but the level is not maintained; fat, however, leads to no elevation in the insulin content above the fasting level but, if anything, occasions a further fall (Best, Haist and Ridout[25] (Fig. 8). It would appear that the insulin

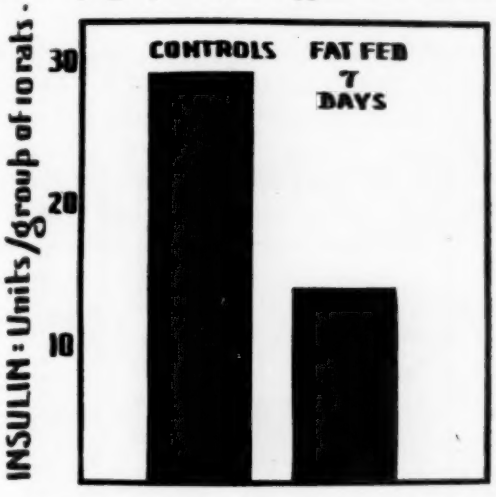


Figure 6. *Total Insulin Units in the Pancreases of Normal and Fat-Fed Rats.*

content of the pancreas is influenced in large part by the amount of available carbohydrate in the diet, although certain other factors are not as yet excluded.

Hypophysectomy and the Effect of Diet

The insulin content of the pancreas in rats hypophysectomized for twenty-six to sixty-six days is not greatly different from that of rats in control groups receiving the same caloric intake, although it is slightly less than that of controls fed *ad libitum* (Haist and Best[6]; Haist[26]). The insulin content of the pancreas of hypophysectomized dogs is not abnormal, according to Chambers, Sweet and Chandler,[27] and we have confirmed this finding in four dogs.

The effect of fat-feeding on the insulin content of the pancreas can still be obtained in hypophysectomized rats (Haist and Best[6]; Haist[26]). When a balanced diet is fed to hypophysectomized rats, previously fed fat for seven days, the insulin content is restored to normal (Fig. 9).

by the administration of insulin. The reduction in the rate of formation of physiologically active insulin is evidently greater than the decrease in the liberation of this material, and as a result the insulin content falls.

The daily administration of insulin to fasting

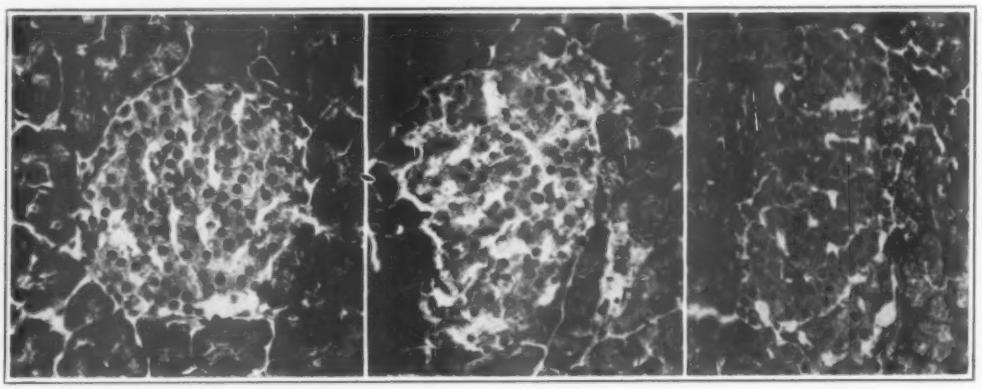


FIGURE 7. *The Histological Differences in the Pancreatic Islets of Normal* (A), *Fasted* (B) *and Fat-Fed* (C) *Rats.*

It would appear that the anterior pituitary gland is essential neither for the action of fat nor probably for that of starvation on the insulin content of the pancreas, although this does not preclude the possibility of some pituitary influence on the mechanism under normal conditions. Islet activity can

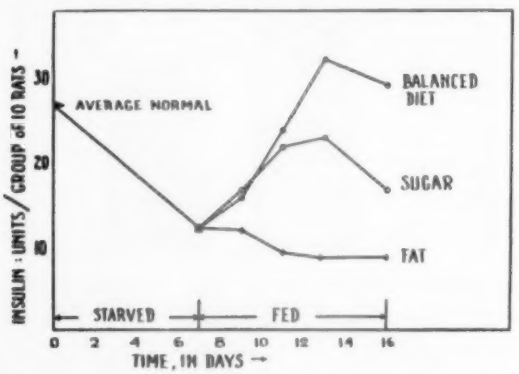


FIGURE 8. *The Effect of Different Diets, Following Starvation, on the Insulin Content of the Pancreas in Rats.*

therefore be depressed and restored in the absence of the pituitary gland.

EFFECT OF INSULIN

Administration of Insulin Greatly Affects the Insulin Content of the Pancreas

When large daily doses of protamine zinc insulin are given to rats fed the same amount of a balanced ration as are control animals, the insulin content of the pancreas is definitely lowered (Haist and Best[28]) (Fig. 10). This observation suggests that the need for endogenous insulin is reduced

rats or to rats fed with fat leads to a much greater reduction in the insulin content of the pancreas than is occasioned by fasting or fat-feeding alone (Haist and Best[6, 28]) (Figs. 11 and 12). It is clear that the administration of insulin does not prevent but increases the effect of fasting or fat-feeding on the insulin content of the pancreas. This should be compared with the effect of administering insulin in animals receiving injections of anterior-

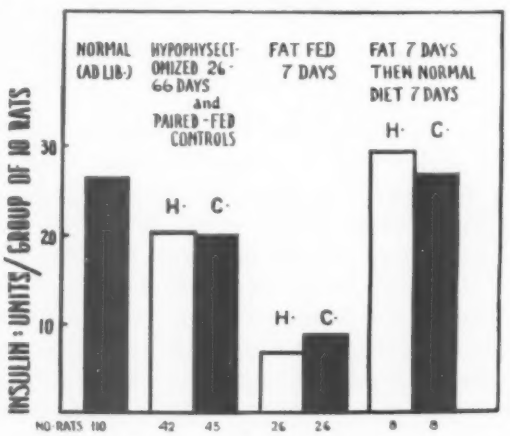

NORMAL (AD LIB.)
HYPOPHYSECTOMIZED 24-66 DAYS and PAIRED-FED CONTROLS
FAT FED 7 DAYS
FAT 7 DAYS THEN NORMAL DIET 7 DAYS
H· C·
INSULIN : UNITS / GROUP OF 10 RATS
30
20
10
NO. RATS 110 42 45 26 26 8 8

FIGURE 9. *The Effect of Diet on the Insulin Content of the Pancreas in Hypophysectomized Rats.*

pituitary extract. In this condition the administration of insulin prevents the fall in insulin content resulting from the injection of the extract (Fig. 13).

The effect of the insulin appears to be similar to that of fasting or fat-feeding and opposite to that of anterior-pituitary extract. The injection of

the latter or the removal of a very large portion of the pancreas makes the islets function more intensively, and may result finally in exhaustion and degeneration of the cells. Under these circumstances the insulin concentration in the pancreas probably falls because the production of insulin can no longer keep pace with its liberation. Fasting, fat-feeding and insulin have an opposite effect. They allow the pancreatic islets to rest and bring about a reduction in the insulin content of the pancreas. The insulin content under these conditions is probably reduced because the production of the hormone is decreased to a greater extent than is its liberation.

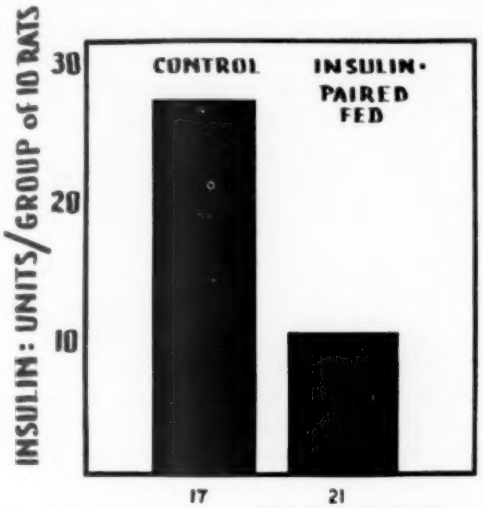


FIGURE 10. *The Effect of Insulin on the Insulin Content of the Pancreas in Normally Fed Rats.*

The numbers under the blocks represent the total number of animals.

Relation to Other Observations on the Effect of Diet and Administration of Insulin

The experiments on rats which we have just cited indicate that fasting, fat-feeding and the administration of insulin not only allow the islets to rest, but also afford an explanation of certain other phenomena that occur when such procedures are employed. It has been known for a long time that changes in the response to administered carbohydrate are apparent in animals fasted or fed with fat for a sufficient period. (For a review of this subject, see Chambers.[29]) Such animals show a reduced tolerance for sugar, as evidenced by the higher, more prolonged blood-sugar curve, glycosuria and the absence of the normal rise in the respiratory quotient following the administration of glucose. The administration of carbohydrate restores the tolerance to normal. Some of these changes have been observed in the hypophysectomized dog.[29]

The alterations in insulin content with changes in diet occur under conditions that should also give rise to changes in tolerance. We have previously referred to the evidence for a reduced activity of the islets under these conditions. This change may affect sugar tolerance in different ways. One possibility is that when the islet activity is reduced, the immediate response of these cells to any sudden increase in the need for insulin is less than normal. An alternative explanation would be that when the level of insulin liberation is low, that is, when the continuous outpouring of the hormone is reduced, the tissues and especially the liver are altered so far as their response to sugar is concerned. Hence it can be seen that regardless of whether the pancreas or the liver is considered to play the major role in determining sugar tolerance, the level of activity of the islet cells may be of great importance. It seems logical to assume that the reduced activity of the islets under the conditions mentioned is in some way responsible for the lowered tolerance to sugar noted under similar conditions. This is substantiated by the fact that insulin administration, which, as previously pointed out, leads to reduced islet activity, also produces a decreased sugar tolerance

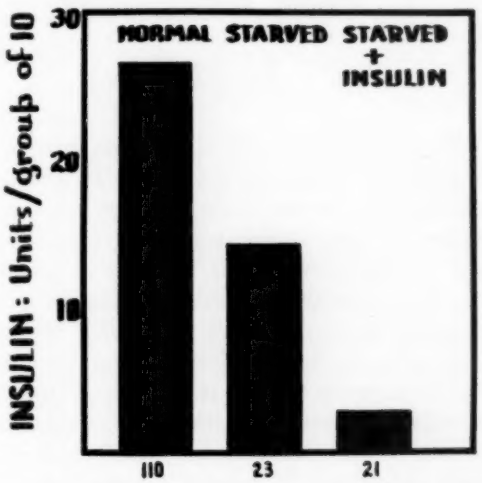


FIGURE 11. *The Effect of Insulin on the Insulin Content of the Pancreas in Fasted Rats.*

(Wilder, Smith and Sandiford[30]; Clark, Gibson and Paul[31]; Maher and Somogyi[32]; Looney and Cameron[33]).

APPLIED PHYSIOLOGY

In considering the relation of our results to the treatment of diabetes in human subjects, we may assume that the factors which prevent the condition from developing will also tend to limit its progress. As we have pointed out, the procedures which permit the pancreatic islets to rest, namely,

fasting, fat-feeding, and the administration of insulin, prevent or hinder the development of the diabetic state under experimental conditions. These procedures affect the pancreas in a manner opposite to that of high-carbohydrate diets, and prevent the deleterious effects of anterior-pituitary diabetogenic principles. There is no evidence as yet that the factors which rest the pancreas cause permanent damage to islet cells, whereas there is adequate proof that factors leading to overactivity may produce permanent changes. If a clinician is convinced that the patient will be benefited

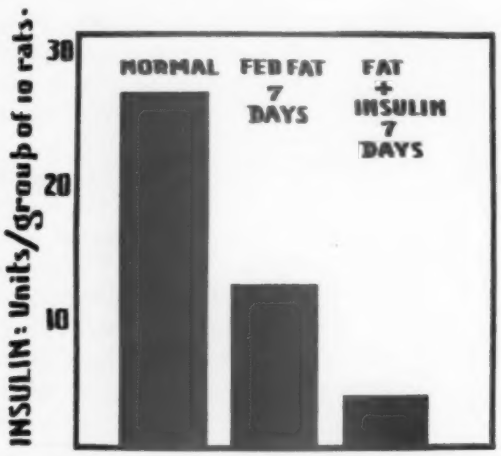


FIGURE 12. *The Effect of Insulin on the Insulin Content of the Pancreas in Fat-Fed Rats.*

by stimulation of the islet cells, diets rich in carbohydrate are obviously indicated. It will be remembered that when such diets are used in experimental animals, the islet cells may be protected by the provision of large amounts of insulin. If, on the other hand, the clinician believes that a useful purpose will be served by resting the pancreas, fasting, fat-feeding and the administration of insulin may be employed. When there is already very extensive islet-cell destruction, he may decide that there is no point in resorting to these procedures. Under other conditions, however, a reduction of the strain on the remaining islets may allow the restoration of some exhausted cells and thus improve the diabetic condition. This would seem to be particularly true in the early stages of the disease. In experimental animals the exhausted cells retain for an appreciable length of time their ability to recover. Lukens and Dohan[19] have obtained evidence that this period is much longer in the cat than it is in the dog. In man, the interval during which the cells may be exhausted but still remain capable of recovery is unknown. It might be argued that a resting or idle beta cell is not much better than an absent one. Temporarily, this may be true. But rest restores the cells and makes possible a better islet function in the future. The resting procedures, then, serve two purposes: they prevent the degenerative changes from occurring in cells not already affected; and they permit the restoration of those exhausted cells which still retain their ability to recover.

If it is thought that protection is needed, the best clinical procedure must be chosen. Wide departures from the normal diet are permissible for only short intervals. Over longer periods nutritional requirements must, of course, be satisfied. This is particularly true for growing children, who must have a palatable diet providing an adequate caloric intake and all the essential food factors. Under these circumstances only minor alterations in diet may be justifiable and the administration of insulin may be the method of choice.

There is considerable evidence that heredity plays an important role in the incidence of diabetes (Pincus and White[34]). A procedure which would allow early diagnosis and treatment in children with a family history of diabetes would be the determination of blood sugars at very frequent intervals. Prevention, however, would be better than

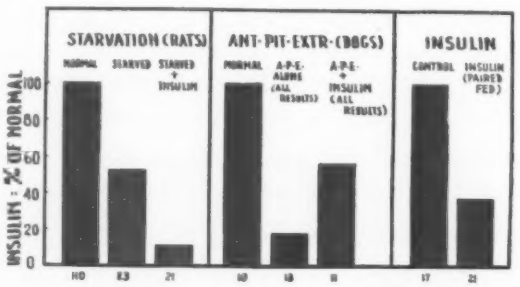


FIGURE 13. *The Effect of Insulin on the Insulin Content of the Pancreas in Different Animals under Varying Conditions.*

cure. The prophylactic administration of insulin to potential diabetic patients may become an accepted clinical procedure in the future. We suggest that the incidence of diabetes should be investigated in two large and comparable groups of children with a family history of this disease. One group should be given a normal diet and the second a diet as low in carbohydrate and protein and as rich in fat as is feasible with the above-mentioned limitations in view. This second group might receive insulin in the limited amounts which may safely be given under these conditions. We appreciate the difficulties inherent in this type of

clinical investigation, but believe that the goal justifies the endeavor.

Summary

Extensive partial pancreatectomy or the daily administration of anterior-pituitary extracts, in dogs, causes a great reduction in the insulin content of the pancreas, which is associated with hydropic degenerative changes in the islets.

Fasting, fat-feeding or insulin administration, in rats, leads to a decrease in the insulin content of the pancreas, but this is not associated with degeneration in the islet cells.

The daily administration of protamine zinc insulin augments the effect of fasting or fat-feeding, giving a still further reduction in the insulin content. It has also been shown that daily injections of protamine zinc insulin in animals receiving anterior-pituitary extract tend to prevent the reduction in the insulin content and the degenerative islet changes produced by the extract alone. The feeding of fat, or fasting, also prevents these effects of the extract.

From these and other considerations mentioned in the paper we conclude that extensive partial pancreatectomy and the administration of anterior-pituitary extract lead to the exhaustion of the islets, largely through overwork, whereas fasting, fat-feeding and insulin administration allow the islets to rest. These latter procedures inhibit the diabetogenic action of the anterior-pituitary extract and thus prevent the onset of diabetes. The clinical applications of these findings are discussed.

It will be clear to all who read this article that the results of recent studies emphasize the great importance of the work which Dr. Frederick M. Allen previously carried out in this same general field. It is a pleasure also to acknowledge the stimulating and helpful influence which Dr. Elliott P. Joslin has exerted on many of us who have attempted to increase the knowledge and understanding of the diabetic state.

References

1. Homans, J.: The relation of the islets of Langerhans to the pancreatic acini under various conditions of secretory activity. *Proc. Roy. Soc., London* Series B86:73-87, 1913.
2. Allen, F. M.: *Studies Concerning Glycosuria and Diabetes.* 1179 pp. Cambridge, Massachusetts: Harvard University Press, 1913.
3. *Idem:* Pathology of diabetes. I. Hydropic degeneration of islands of Langerhans after partial pancreatectomy. *J. Metabolic Research* 1:5-41, 1922. Pathology of diabetes. IV. Role of hyperglycemia in production of hydropic degeneration of islands of Langerhans. *Ibid.* 1:75-88, 1922.
4. Copp, E. F. F., and Barclay, A. J.: The restoration of hydropically degenerated cells of the pancreatic islands in dogs under insulin treatment. *J. Metabolic Research* 4:445-451, 1923.
5. Bowie, D. J.: unpublished data.
6. Haist, R. E., and Best, C. H.: Factors affecting the insulin content of pancreas. *Science* 91:410, 1940.
7. Richardson, K. C., and Young, F. G.: Histology of diabetes induced in dogs by injection of anterior-pituitary extracts. *Lancet* 1:1098-1101, 1938.
8. Best, C. H.; Campbell, J., and Haist, R. E.: The effect of anterior pituitary extracts on the insulin content of the pancreas. *J. Physiol.* 97:200-206, 1939.
9. Ham, A. W., and Haist, R. E.: Histological effects of diabetogenic anterior pituitary extracts. *Nature* 144:835, 1939.
10. Houssay, B. A.; Biasotti, A., and Rietti, C. T.: Action diabétogène de l'extrait anté-hypophysaire. *Compt. rend. Soc. de biol.* 111:479-481, 1932.
11. Houssay, B. A., and Potick, D.: Antagonisme entre l'hypophyse et l'insuline chez le crapaud. *Compt. rend. Soc. de biol.* 101:940-942, 1929.
12. di Benedetto, E.: Extrait antéro-hypophysaire et résistance à l'insuline. *Compt. rend. Soc. de biol.* 112:499-501, 1933.
13. Cope, O., and Marks, H. P.: Further experiments on the relation of the pituitary gland to the action of insulin and adrenaline. *J. Physiol.* 83:157-176, 1935.
14. Campbell, J.; Haist, R. E.; Ham, A. W., and Best, C. H.: The insulin content of the pancreas as influenced by anterior pituitary extract and insulin. *Am. J. Physiol.* 129:328, 1940.
15. Houssay, B. A.: Diabetes as a disturbance of endocrine regulation. *Am. J. M. Sc.* 193:581-606, 1937.
16. Young, F. G.: The anterior pituitary gland and diabetes mellitus. *New Eng. J. Med.* 221:635-646, 1939.
17. Marks, H. P., and Young, F. G.: Observations on the metabolism of dogs made permanently diabetic by treatment with anterior pituitary extract. *J. Endocrinology* 1:470-510, 1939.
18. Dohan, F. C., and Lukens, F. D. W.: Further observations on the permanent diabetes produced by anterior pituitary extract. *Am. J. Physiol.* 126:478, 1939.
19. Lukens, F. D. W., and Dohan, F. C.: Morphological and functional recovery of the pancreatic islands in diabetic cats treated with insulin. *Science* 92:222, 1940.
20. Richardson, K. C.: The influence of diabetogenic anterior pituitary extracts on the islets of Langerhans in dogs. *Proc. Roy Soc., London* Series B128:153-169, 1940.
21. Anselmino, K. J.; Herold, L., and Hoffmann, F.: Ueber die pankreatrope Wirkung von Hypophysenvorderlappenextrakten. *Klin. Wchnschr.* 12:1245-1247, 1933.
22. Richardson, K. C., and Young, F. G.: The "pancreotropic" action of anterior pituitary extracts. *J. Physiol.* 91:352-364, 1937.
23. Marks, H. P., and Young, F. G.: The hypophysis and pancreatic insulin. *Lancet* 1:493-497, 1940.
24. Haist, R. E.; Ridout, J., and Best, C. H.: Diet and the insulin content of the pancreas. *Am. J. Physiol.* 126:518, 1939.
25. Best, C. H.; Haist, R. E., and Ridout, J.: Diet and the insulin content of pancreas. *J. Physiol.* 97:107-119, 1939.
26. Haist, R. E.: The pituitary and the insulin content of pancreas. *J. Physiol.* 98:419-423, 1940.
27. Chambers, W. H.; Sweet, J. E., and Chandler, J. P.: Carbohydrate metabolism in the hypophysectomized dog. *Am. J. Physiol.* 113:26, 1935.
28. Haist, R. E., and Best, C. H.: unpublished data.
29. Chambers, W. H.: Undernutrition and carbohydrate metabolism. *Physiol. Rev.* 18:248-296, 1938.
30. Wilder, R. M.; Smith, F. H., and Sandiford, I.: Observations on obesity. *Ann. Int. Med.* 6:724-742, 1932.
31. Clark, B. B.; Gibson, R. B., and Paul, W. D.: A study of the role of insulin in metabolism in nondiabetic patients. *J. Lab. & Clin. Med.* 20:1008-1016, 1935.
32. Maher, J. T., and Somogyi, M.: Effect of insulin on carbohydrate tolerance of nondiabetic individuals. *Proc. Soc. Exper. Biol. & Med.* 37:615-618, 1937.
33. Looney, J. M., and Cameron, D. E.: Effect of prolonged insulin therapy on glucose tolerance in schizophrenic patients. *Proc. Soc. Exper. Biol. & Med.* 37:253-257, 1937.
34. Pincus, G., and White, P.: On the inheritance of diabetes mellitus: analysis of six hundred and seventy-five family histories. *Am. J. M. Sc.* 186:1-14, 1933.

THYROGLOSSAL CYSTS AND SINUSES*

A Study and Report of 198 Cases

ROBERT E. GROSS, M.D.,† AND MARION L. CONNERLEY, M.D.‡

BOSTON

MIDLINE cervical cysts and sinuses arising from the thyroglossal duct are often encountered in childhood. These lesions are of importance because of disfigurements which they produce

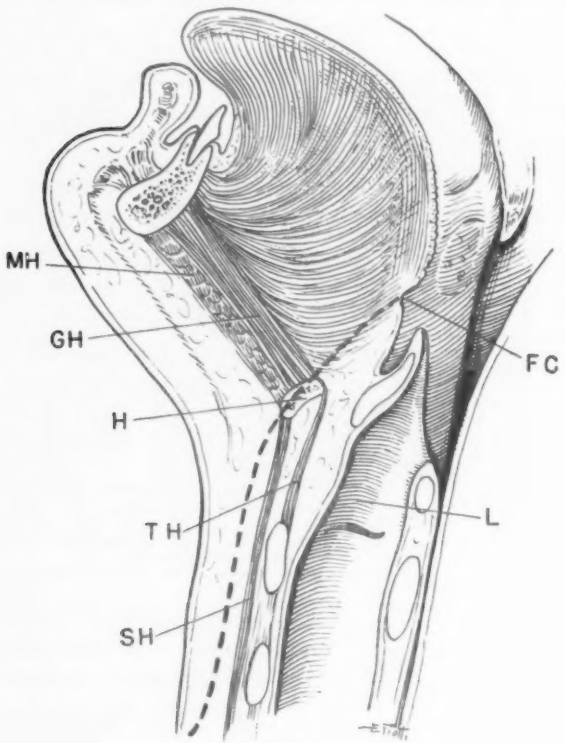


FIGURE 1.

Sagittal section through the tongue, larynx and neck, showing the position of structures related to thyroglossal cysts and sinuses which may occur anywhere along the dotted line. FC = *foramen cecum;* GH = *geniohyoid muscle;* H = *hyoid bone;* L = *larynx;* MH = *mylohyoid muscle;* SH = *sternohyoid muscle;* TH = *thyrohyoid membrane.*

and because they may be the seat of recurring inflammatory disease. It is the purpose of this paper to review and report the findings from 198 cases observed or treated at the Children's Hospital.

EMBRYOLOGICAL CONSIDERATIONS

In embryos of 1.5 or 2.5 mm., the thyroid anlage appears as a midline structure projecting downward between the first and second branchial arches. The stalk of this anlage has an attachment at the tuberculum impar, which later becomes the foramen cecum. The thyroid anlage descends in the neck but maintains its superior connection by the long thyroglossal duct. Toward the latter half of the second month, the developing hyoid bone divides the thyroglossal duct into upper and lower portions which subsequently atrophy and disappear by the end of the eighth week. Rests of cells may remain anywhere along this tract and give rise to postnatal development of cysts (Fig. 1). By pressure necrosis of overlying skin or by suppuration during a superimposed inflammation, such a cyst may attain an external cutaneous opening and thereby be transformed into a fistula.

PATHOLOGY

Thyroglossal cysts or sinuses are lined by an epithelium which is usually columnar or ciliated, but which may be squamous in type. Like the cysts, the sinuses may have a flat and rather level epithelial lining, but not uncommonly there are small slit-like or irregularly branched side pockets extending for several millimeters into the surrounding tissues. The cyst or sinus usually contains some mucoid material which has been secreted by its lining cells; but if squamous cells form a part of the epithelial lining, yellow grumous or pasty material may be found in the lumen. Varying degrees of acute and chronic inflammation are found in the walls, particularly those of the sinuses.

Microscopic sections of the central part of the hyoid bone from these cases often show an irregular or branching epithelium-lined tract directly piercing the bone or its periosteum. It may be impossible to detect this abnormality by gross inspection, palpation or probing. Likewise, study of soft tissues removed *en bloc* above or below the hyoid bone, and yet above the gross cyst or sinus, often shows microscopic-sized tracts which were unsuspected by the surgeon. The thorough operator, therefore, must always remove a block of tissue upward as far as the foramen cecum and must remove the central part of the hyoid bone, even though he cannot see or feel any tract in these structures.

*From the Surgical Clinic, Children's Hospital, and the Department of Surgery, Harvard Medical School.

This publication was aided by a grant from the Godfrey M. Hyams Trust.

†Associate in surgery, Harvard Medical School; associate visiting surgeon, Children's Hospital.

‡Surgical house officer, Children's Hospital.

Clinical Findings

In approximately 85 per cent of our patients the lesions were cysts, and in about 15 per cent they were sinuses. In a few cases there was a cyst in the deeper portions of the neck and a superficial sinus which opened on the skin. Such a sinus may or may not connect with the cystic structure.

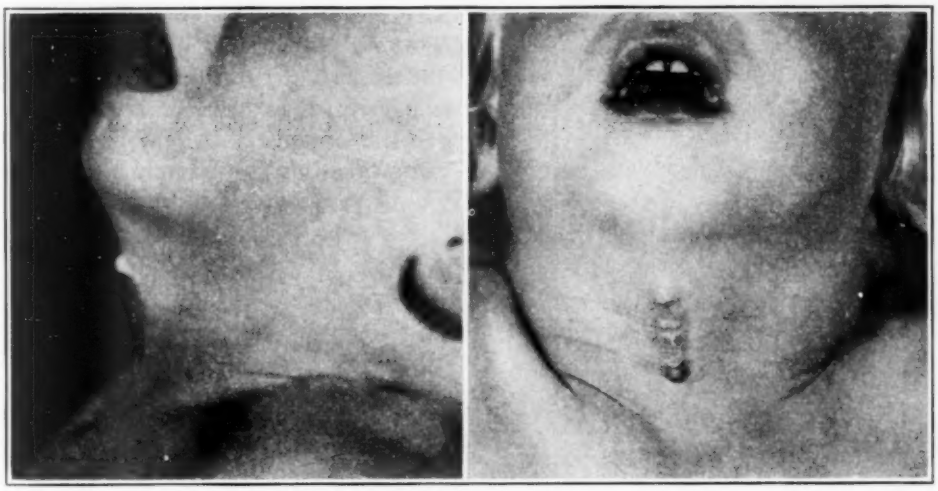


Figure 2.

A five-year-old girl with a vertical, midline, reddened area of mucous membrane which had been present since birth. This represents a thyroglossal sinus which has extensively opened along its anterior edge, thus presenting the mucous membrane to view.

In some cases a midline cyst had been present for a considerable period of time before it subsequently attained a cutaneous opening. In 2 cases there were vertical midline linear cutaneous lesions, in each of which a long sinus appeared to have opened anteriorly so as to expose a long piece of raw mucous membrane (Figs. 2 and 3).

A thyroglossal cyst may be found anywhere in the midline cervical structures from the base of the tongue downward to the suprasternal notch (Figs. 4 and 5). The cyst may be as small as a pea, or as large as a flattened golf ball. An average cyst is 1 to 2 cm. in diameter (Fig. 6). In general, the cysts are smoothly rounded and have a well-defined border, but the larger ones are apt to be compressed by overlying skin or fascia. The larger cysts can be moved only slightly, but the smaller ones can be readily displaced upward and downward and also from side to side. As a rule they are nontender, unless there has been some superimposed infection. Almost invariably there is some deep attachment to structures in the base of the mouth or to the underlying hyoid bone, whereas they are unattached to the overlying skin. In rare cases pressure on the cyst will express a small amount of fluid into the throat by way of a tract leading to the base of the tongue. If the cyst is freely movable it may not ride directly in the midline but slide off slightly to one side of the trachea or the larynx (Fig. 7). Because of the overlying cervical fascia, the cysts usually do not transilluminate well, in spite of the fact that they may contain clear fluid.

In 3 cases there was a small swelling at the base of the tongue, for treatment of which the patients entered the Nose and Throat Department. These proved to be thyroglossal cysts 0.8 to 1.5 cm. in diameter which lay just beneath the foramen cecum.

Thyroglossal-duct sinuses open in the midline anywhere from the suprasternal notch upward to a position just in front of the hyoid bone. In most cases careful palpation of the neck will reveal a cord of tissue running upward in the deep structures of the neck, and an attachment to the hyoid bone can often be made out. The cutaneous openings are from 1 to 3 mm. in diameter (Fig. 8). The skin around the opening usually shows some degree of chronic inflammation. From time to time, droplets of fluid, which are either clear, glairy and mucoid or cloudy, thin and yellowish, may exude from the sinus. The latter type of fluid may be purulent exudate or may be desquamated cells from a squamous epithelial lining. Therefore, a yellowish discharge does not necessarily mean that infection is present.

Figure 9 shows the year in which a cyst or sinus was first noted in our 110 patients who were subsequently operated on. In 29 per cent of the cases the lesions were noted at birth, and in 76 per cent

the symptoms began before the sixth year. Some patients entered the hospital shortly after the abnormality was noticed, but in the majority of

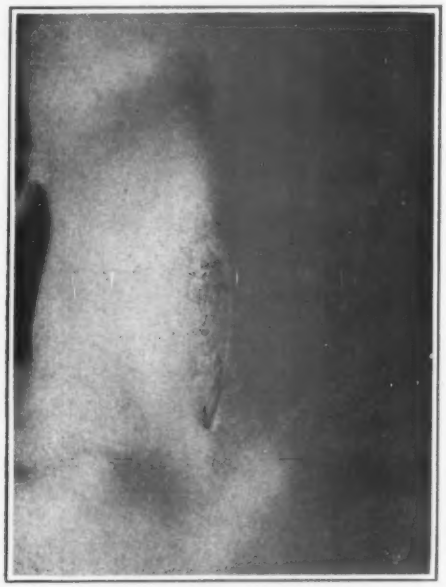


FIGURE 3.

An eleven-year-old girl with a raw vertical elliptical lesion which had been observed since birth. At the lower end of the elliptical area a small sinus orifice can be seen, which led downward 1 cm. into the neck. At operation there was also a cord of tissue running from the upper end of the cutaneous lesion to the hyoid bone.

cases there was a lapse of many months or years before treatment was undertaken. In 4 cases the parents had noticed no abnormality in the neck until a respiratory infection had produced inflammation in a small cyst and had thereby suddenly augmented its size.

Thyroglossal-duct sinuses and cysts are slightly commoner in girls than in boys, the respective proportions in the present series being 56 and 44 per cent.

DIFFERENTIAL DIAGNOSIS

Acute suppurative or nonsuppurative submental adenitis usually gives no difficulty in the differential diagnosis, because the origin of the infection in the teeth, the lower lip or the chin is obvious. Furthermore, the inflammatory lesion in the submental region is more anterior in location than are the remnants of the thyroglossal system.

Branchiogenic cysts should rarely give difficulty in differentiation. These have a more lateral position, tending to occur along the anterior border of either sternomastoid muscle. While a thyroglossal cyst may slide off slightly to one side of the trachea, it is never displaced far enough to be confused with a branchiogenic cyst. Branchiogenic sinuses always have a lateral cutaneous opening, while thyroglossal sinuses invariably open in the midline.

If a thyroglossal sinus has a cutaneous opening below the level of the thyroid isthmus it may be confused with suppurative lesions, usually tuberculous, arising in the mediastinum which have dissected upward. It is therefore obvious that all patients with a sinus opening below the level of the thyroid isthmus should be roentgenologically examined in order to exclude the possibility of tuberculosis of the lungs or of the bronchial lymph nodes.

Lipomas of the neck are rare. They tend to be slightly lobulated and less spherical than the thyroglossal cysts and on the basis of this finding can usually be differentiated therefrom.

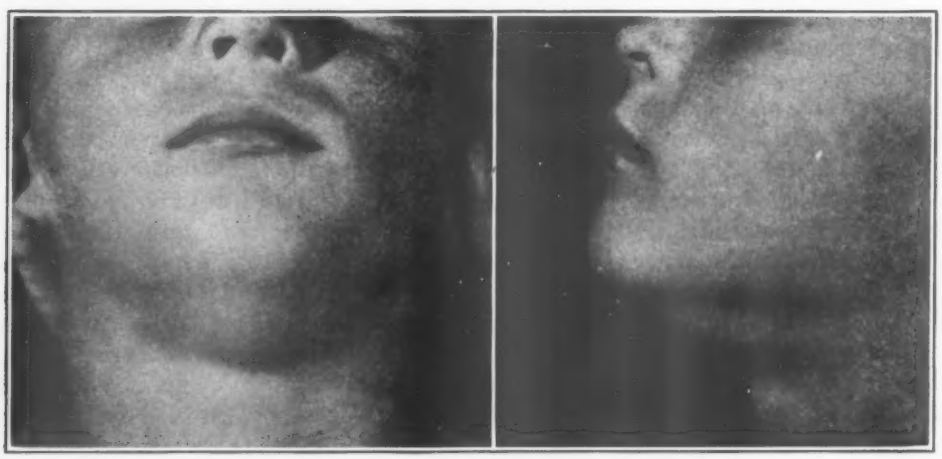


FIGURE 4.

An eight-year-old boy with a high anterior thyroglossal cyst which had been noticed for four years.

Dermoid or sebaceous cysts in the midline of the neck are attached to the overlying skin, in contrast to the thyroglossal cyst, which has a deep anchorage.

Treatment

Before considering treatment in these cases, it is well to state that we do not believe that all thyroglossal cysts should be removed. During the period in which our 110 cases have been surgically treated, 88 additional patients who presumably had small thyroglossal cysts have been examined and observed, and have not been operated on. In these cases operation was advised against because the cysts did not enlarge appreciably or because disfigurement was minimal. It is possible that some of these patients may come to subsequent surgery. While we have thus deferred operation for these small cysts, we have always advised operative excision of the sinuses because of the high probability of recurring infection.

We do not believe in the treatment of thyroglossal sinuses or cysts by the use of sclerosing or cauterizing agents, because it is unreasonable to expect that injected fluids will reach all the epithelial-lined side pockets that can be found on histological examination of many of these specimens.

In 11 of our patients an infected and suppurating cyst had to be incised and drained before radical removal could be undertaken.

Since all the treated cases in this series were children, general anesthesia, either by ether or by Avertin and ether, was employed. However, in older age groups local or block anesthesia would undoubtedly be satisfactory. With the patient lying on the table, the trunk should be slightly raised and the head well extended. Midline vertical incisions are contraindicated because the subsequent scar is unsightly and a midline contracture which is extremely difficult or impossible to eradicate may result. A transverse incision should always be made and great care employed in the selection of the site of the incision, in order to make sure that it exactly falls in the folds of the neck and extends equidistantly to each side of the midline. The incision can rarely be shorter than 2 cm. if good exposure is to be obtained in the deeper portions of the neck, and it may have to be twice this length if the child is large or the cyst is big. If a cutaneous sinus is present, a transverse elliptical incision is made so as to include the cutaneous orifice. Freeing the cyst or sinus usually offers no difficulty unless there has been severe inflammation in the regional tissues.

For the inexperienced operator there is often a temptation to remove only the presenting cyst or the presenting sinus as far as the hyoid bone. There are doubtless some cases in which this incomplete procedure will result in permanent cure. However, we and others have learned that to do this leads frequently to recurrences

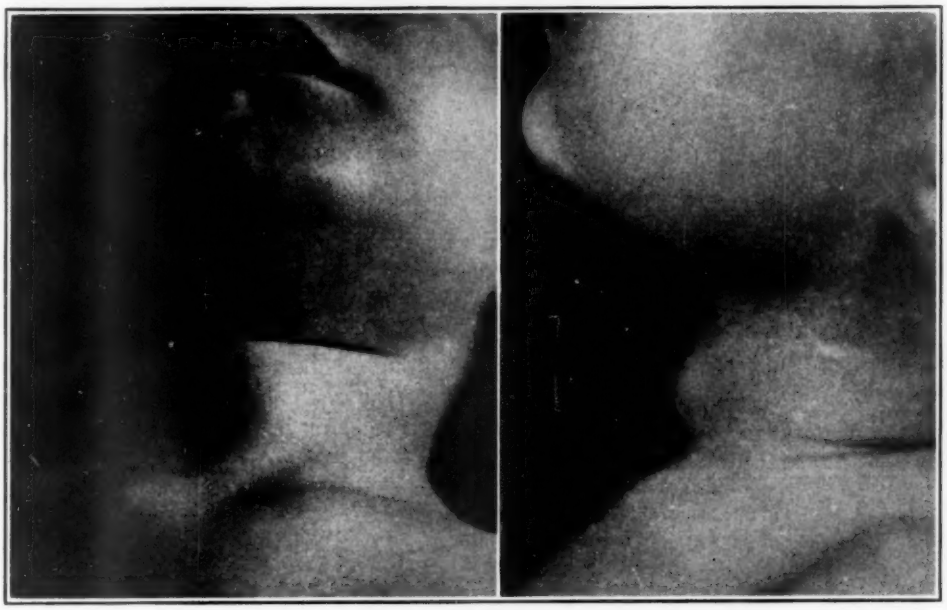


Figure 5.

A four-year-old girl with a small, low, thyroglossal cyst which had been present for one year.

which are more difficult to handle at secondary operations. Therefore, it cannot be emphasized too strongly that the only proper treatment must always include removal of about 1 cm. of the hyoid bone and in addition a block of tissue up to the base of the tongue. This more extensive operation does not appreciably increase the length of the operation, and if it is routinely carried out, recurrences will be rare; indeed they were absent in our series.

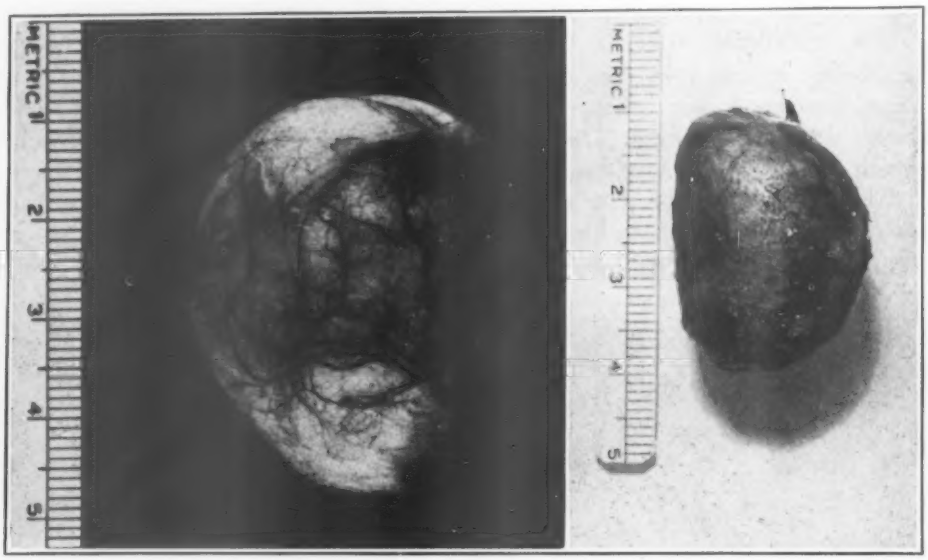


FIGURE 6.
Photographs of surgically removed thyroglossal cysts.

Figure 10 indicates the successive operative steps. In *1* there is a transverse incision over a presenting midline cyst. In *2* this has been carried down through subcutaneous fat and platysma muscle. In *3* the cyst is grasped with a clamp and exteriorized to show better the deep cervical fascia which extends up over the cyst. This fascia is cut around the base of the cyst, so that a stalk is brought into view as shown in *4*. In *5* the presenting muscles are cleared from the overlying structures

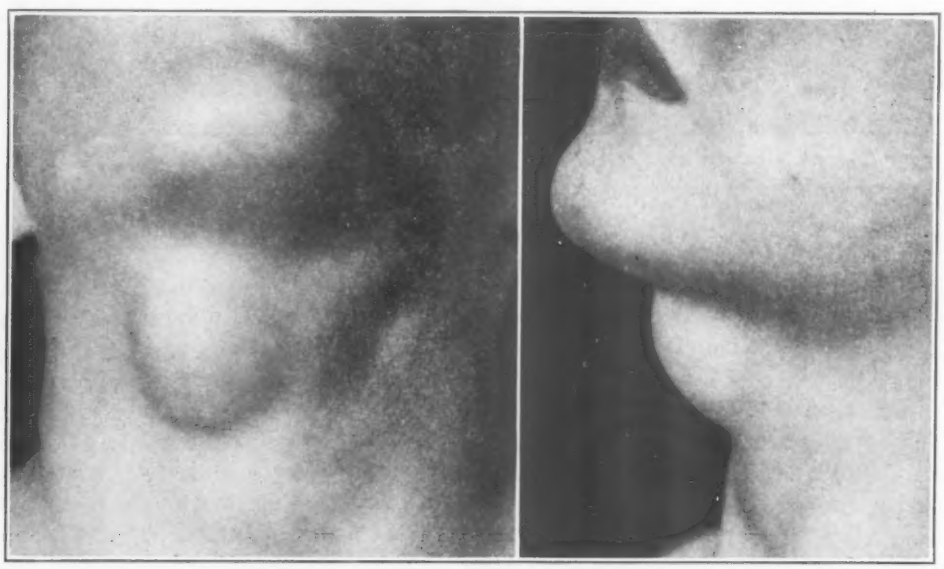


FIGURE 7.
A five-year-old girl with a thyroglossal cyst which had been present for three years. In the anterior view the cyst is seen to be displaced slightly from the midline.

and the fibers of the mylohyoid muscles of either side can be seen coursing obliquely to meet in the midline. Below the stalk, the longitudinal fibers of the ribbon muscles (sternohyoid) are brought into view. At the junction of these two groups of muscles the hyoid bone is now seen or palpated. In young subjects the external surface of the bone can be viewed, but in more muscular or older individuals the hyoid bone may be more deeply imbedded. In *6* the hyoid bone is grasped with an Allis clamp just to one side of the midline and the bone is pulled forward. It is then cut with a scalpel in the patients less than two or three years of age, but it must be severed with bone cutters in older subjects. In *7* the hyoid bone has been cut on both sides and traction on the cyst will pull forward the centrally freed portion of hyoid bone. One blade of the scissors can then be pushed inward as far as the thyrohyoid membrane and a circular cut of all the muscles can be rapidly made, so that a fringe of musculature is left on the centrally placed block of tissue. If one does not know the regional anatomy well, there may be some hesitation at this step, for fear of entering the mouth. However, the thyrohyoid membrane is a distinct grayish-yellow structure which can be readily identified and dissected from the overlying musculature. Rather than make many cuts through the muscles to get down to this membrane, it is best to puncture through the muscles at one point as far as the membrane, and then to sweep the scissors around, severing a full thickness of musculature in each cut. In *8* the thyrohyoid membrane forms the floor of the wound, and attached to it is a stalk of tissue, as shown. A forefinger of the anesthetist or an assistant, passed into the mouth and pressing in the region of the foramen cecum, will show that the base of the stalk is separated from the finger in

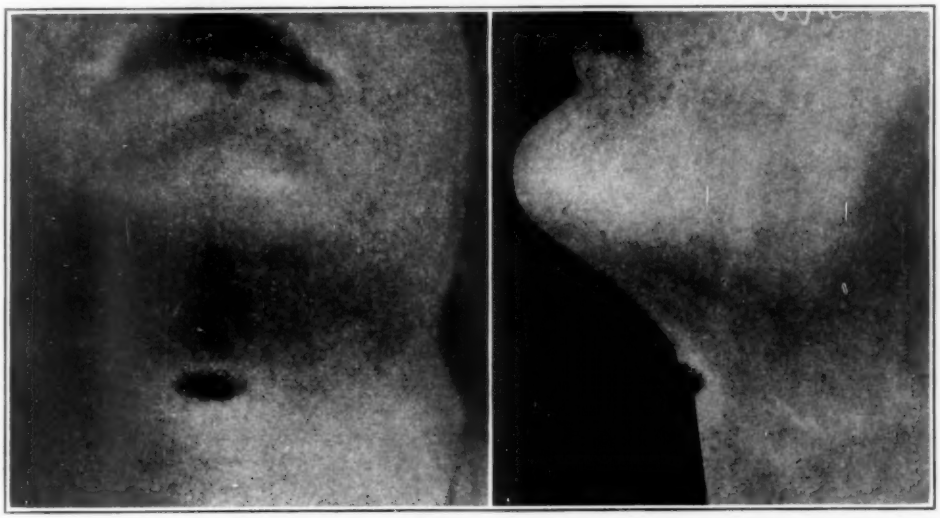


FIGURE 8.

A ten-year-old girl with a thyroglossal-duct sinus. The discharging fistula had been noted for three years.

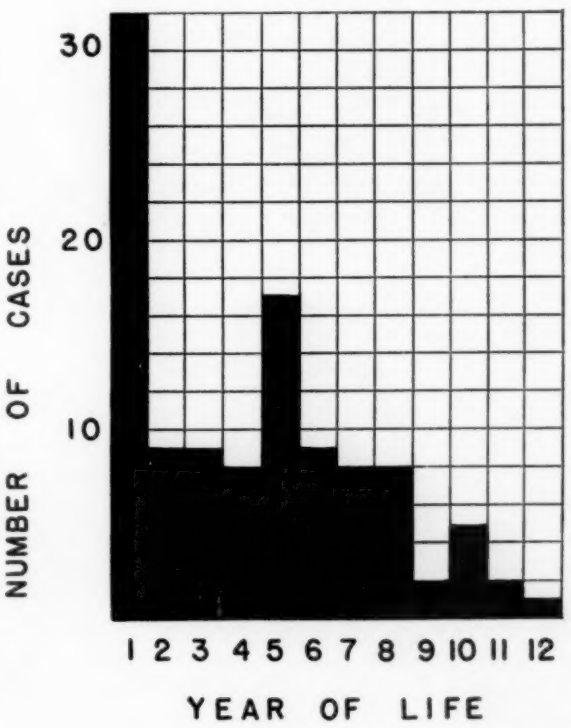


FIGURE 9.

A graph showing the ages at which symptoms were first noticed in 110 surgically treated cases of thyroglossal cyst or sinus. Seventy-six per cent of the patients had symptoms before they were six years of age.

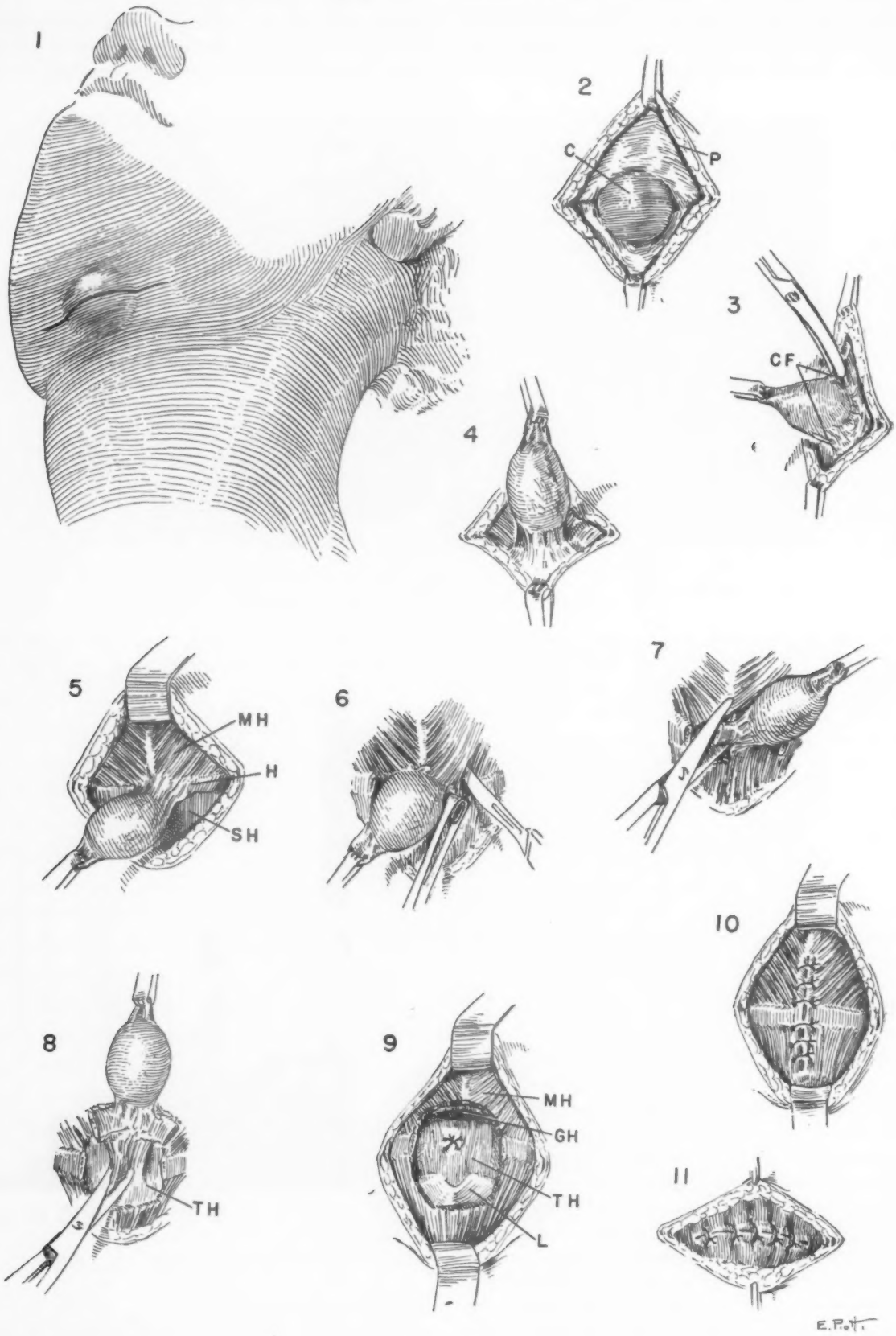


FIGURE 10.

Sketch of the steps in the operative removal of a thyroglossal cyst (or sinus), which are described in the text. C = *cyst;* CF = *cervical fascia;* GH = *geniohyoid muscle;* H = *hyoid bone;* L = *larynx;* MH = *mylohyoid muscle;* P = *platysma muscle;* SH = *sternohyoid muscle;* TH = *thyrohyoid membrane.*

the mouth by only a few millimeters of tissue. When the dissection has been carried to this complete extent the stalk may be cut across. In *9* a figure-of-eight suture or a purse-string suture is placed so as to invert the local tissue into the mouth. In *10* the musculature is brought together in the midline with interrupted sutures of fine silk or fine chromic catgut. No attempt need be made to approximate the ends of the bone, and indeed, even if they do not butt against one another no subsequent derangement in the action of the local muscles will be noticed. In *11* the platysma muscle has been approximated in a transverse manner. The skin may be closed with sutures of fine silk or clips, but we have obtained the best cosmetic results with a continuous subcuticular stitch of fine (No. 00000) Kaldermic suture material on an atraumatic needle. This stitch is removed in seven or eight days and the resulting hairline scar is almost invisible. If hemostasis has been adequate no drainage need be employed.

The technic described above is also used in the excision of a thyroglossal sinus. The tract must be followed upward, and even though a cord cannot be palpated, a complete block of tissue 5 to 7 mm. in diameter must be removed all the way to the base of the tongue, with the invariable excision of the central portion of the hyoid bone.

Patients with an exposed midline piece of mucous membrane, as shown in Figures 2 and 3, are extremely difficult to handle, principally because a vertical elliptical incision must be employed. In these cases it is again always advisable to remove a complete block of tissue to the base of the tongue. The vertical approximation of the platysma muscle and skin may give an excellent immediate cosmetic result, but these wounds have a great tendency to keloid formation and contracture.

A word of caution must be given concerning the removal of an ectopic thyroid gland which has been mistaken for a thyroglossal cyst. Such an accident has occurred in one case at this hospital (Fig. 11), and it is pertinent to record the lessons learned therefrom. To avoid such an unfortunate experience, two rules should be adopted. First, if there is any question about the cyst's containing solid tissue, it should be opened before completely detaching it from its bed. If it is found to contain thyroid tissue, it can be left in its abnormal position in the neck and the wound closed. Secondly, if high midline thyroid tissue is found, it should not be removed without ascertaining that a normally placed thyroid gland is also present. It will usually be found impossible to dissect downward from the high neck wound in order to obtain this information; hence it is justifiable to make a small transverse midline incision 1.0 to 1.5 cm. long over the thyroid isthmus so as to expose and positively identify the thyroid gland. Making this second exploratory incision is far preferable to producing myxedema by blindly and unhesitatingly removing a high ectopic thyroid gland. It is seldom that these considerations must be borne in mind, but they should be remembered by anyone who treats thyroglossal-duct lesions.

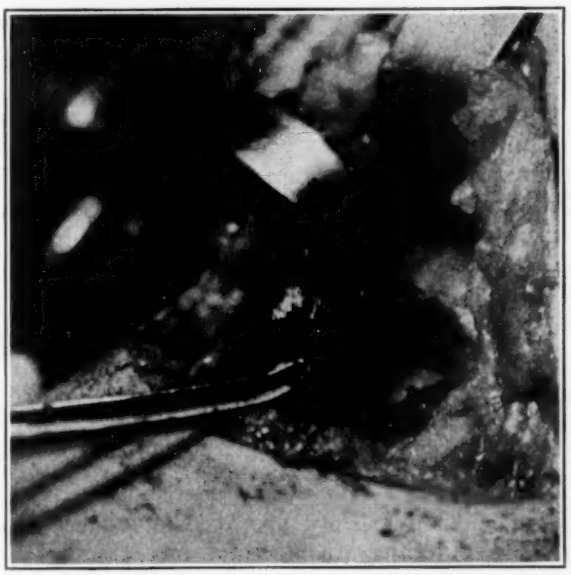


FIGURE 11.

Operating-table photograph of a dissected specimen which was thought to be a thyroglossal cyst, but which later proved to be an ectopic thyroid gland. The child subsequently developed myxedema, necessitating administration of thyroid.

RESULTS OF TREATMENT

Three of our cases were successfully treated by intraoral procedures, since the cysts presented in the mouth at the base of the tongue. Ninety-one cases were treated by the complete operative procedure, which included removal of the middle of the hyoid bone. None of these patients have had a recurrence. In 16 cases incomplete operative procedures were done, in which a portion of the hyoid bone was not removed or insufficient tissue was removed above the hyoid bone. Eight of these patients have shown no evidence of recurrence, but the other 8 have had subsequent formation of a cyst. Six of the recurrences were subjected to secondary or tertiary procedures before a final cure was obtained, and 2 patients refused

to have subsequent treatment. The 2 patients with a midline exposed mucous membrane have not had good cosmetic results, and because of these experiences we are convinced that such cases should have routine excision followed by x-ray therapy four to seven days after operation, in order to abolish or reduce keloid formation.

SUMMARY

The clinical findings from 198 children with thyroglossal cysts or sinuses are summarized. If a thyroglossal cyst is small, if disfigurement is minimal, and if inflammation has not occurred, surgical therapy may be omitted or deferred. If the cyst is large it should be removed in order to improve the cosmetic appearance and to lessen the danger of the superimposed infection that is apt to follow All thyroglossal-duct sinuses should be surgically removed because they are a source of recurring inflammatory disease.

Operative treatment should always include resection of the central part of the hyoid bone and also removal of a block of tissue upward as far as the base of the tongue. Less complete operation will often effect cures, but to ensure against recurrences the more extensive procedure should always be done. The results of treatment in 110 surgically treated cases are summarized.

300 Longwood Avenue

ECZEMA IN INFANTS AND YOUNG CHILDREN*

LEWIS WEBB HILL, M.D.†

BOSTON

ECZEMA in infants and young children may be caused by allergy to foods, to inhalants, to organic or inorganic contactants, to fungous or low-grade pyogenic infection, or to chemical or mechanical irritation. The clinical picture and, above all, the search for the etiologic factor are therefore complicated. It is probably true, however, that most cases develop on an allergic soil, and discussion will be confined to this group.

Typical allergic eczema, or "atopic dermatitis," as it is now often called, seldom begins before the age of three months. The clinical picture may be quite variable, for although the typical lesion is a small exudative papule, there may instead be diffuse erythema, macules, vesicles or even wheals, and added to these, crusts, pustules, fissures or ulcers, the result of secondary changes due to trauma or infection. As a rule the lesions of atopic dermatitis do not have sharp margins, and if nummular or serpiginous flat lesions with sharp margins are seen, and there is not much itching, the chances are that one is not dealing with atopic dermatitis. This does not always hold, however.

The diagnosis of atopic dermatitis in an infant is suggested by the character of the eruption and the severe itching, and may often be confirmed by positive skin tests. Normal infants may give a positive intracutaneous reaction for a short time after eating a new food: they do not give positive scratch-test reactions at any time, so that if such a reaction is obtained one can be sure that the infant is allergic, and that the basis of the dermatitis, at any rate, is of that nature. It is not uncommon, however, for infection with yeast-like organisms or with ordinary pyogenic cocci to be superimposed on an atopic dermatitis, and ammonia dermatitis of the buttocks is also common in these infants, so that sometimes the skin lesions seen in one case may in reality represent two or three different diseases. It should be remembered that not all so-called "eczema" is atopic dermatitis, and that not all atopic dermatitis is due to food alone.

Treatment in the main is fairly but by no means entirely satisfactory; the baby can as a rule be made more comfortable, and the skin can be improved. Prompt and spectacular cure is, however, uncommon, although it can take place. A combination of immunologic and local treatment is much better than either alone. The immunologic treatment consists in determining by the history and skin tests the allergens to which the infant is sensitized, and removal of these from the diet or environment. It must be remembered, however, that not all positive skin tests are of etiologic significance: some infants are able to take with impunity foods to which they give positive tests; others are promptly improved or cured when some food to which they react is removed from the diet, and as promptly break out again when it is resumed. The differentiation between etiologic and non-etiologic skin tests is one of the most perplexing and least understood questions in allergy. There can be no doubt that many infants are relieved of their dermatitis when certain foods,

*This and the two subsequent papers were presented at a meeting of the Section on Pediatrics at the annual meeting of the Massachusetts Medical Society, Boston, May 21, 1940.

†Associate in pediatrics, Harvard Medical School; visiting physician, Children's and Infants' Hospitals.

notably milk and wheat, are removed from the diet.

It is not at all uncommon, however, particularly in the severer cases with erythrodermia, to remove all foods to which there are positive skin reactions and yet to see no improvement whatever. There is a wide gap in knowledge here, which needs filling in before this disease can ever be really understood. It is quite true that it develops on an allergic soil — there can be no argument about that. The relation of specifically sensitizing allergens to the production of the dermatitis is quite another question. Sometimes the cause-and-effect relation is quite clear; many times it is not clear at all.

Most babies with atopic dermatitis give positive skin reactions to egg white. This is probably of no direct etiologic significance, for these babies are not eating egg, although some have thought that the egg antibodies fixed in the skin cells cause the dermatitis, without intervention of antigen. About two thirds of the egg-sensitive infants will be made violently ill if they eat it, or are sent into shock if it is injected parenterally; for about a third it is harmless, in spite of positive skin tests. The origin of this early sensitivity to egg is not entirely clear: the most commonly held view is that it takes place in utero.

Milk and wheat are the two most important allergens concerned in the production of atopic dermatitis in infancy. Positive scratch tests to milk are, however, not very common, and the intracutaneous test must often be used to demonstrate sensitivity. A positive scratch test is usually of etiologic significance; a positive intracutaneous test may or may not be.

In dealing with milk sensitivity in eczema, goat's milk or a milk-free food may be of value; in my experience evaporated cow's milk is not often so. The objection to goat's milk is that there are often crossed reactions between it and cow's milk, so that the infant may be as sensitive to the former as to the latter. The disadvantage of the milk-free foods, most of which are made of soybean flour, is that they sometimes cause bulky, loose bowel movements and irritated buttocks. If the formula is cooked in a double boiler for three quarters of an hour, this tendency is considerably lessened. The use of goat's milk and of milk-free foods in the dietetic treatment of infantile eczema is common. They sometimes do a great deal of good. Often, however, they do none whatever, for they are unfortunately used indiscriminately in all sorts of cases whether or not there is milk sensitivity, or even in patients whose dermatitis has nothing to do with allergy. They are of possible benefit only in patients who have eczema because they are hypersensitive to cow's milk.

Wheat is the most allergenic of the cereals, and positive skin reactions to it in eczematous infants are usually significant. The present practice of feeding large amounts of wheat cereal to infants at an early age has probably increased the incidence of sensitization to wheat. It is very uncommon for any of the antirachitic oils to have an etiologic relation to eczema, and there is therefore rarely any need to omit oil from the diet as is so often done. Orange juice is somewhat likelier to cause trouble. Even if skin reactions to orange are negative, it is not uncommon for itching to be severer after taking it. Of the vegetables, peas and spinach are the most allergenic.

Sensitivity to environmental allergens is not so common in infants as it is in older children, but should be considered. Sensitivity to feathers is not uncommon, and it is well not to allow an eczematous infant to sleep on a feather pillow. Silk and kapok are occasionally causes of dermatitis.

Local treatment is essential in all cases. First and foremost, it must be remembered that the dermatitis must be given a chance to heal; it can never do so if there is continual rubbing and scratching. There is no method of restraint that is entirely satisfactory; aluminum mitts are fairly effective. Face masks I no longer recommend. A rectangle of cellophane taped to the part of the bed sheet underneath the head is valuable in preventing trauma due to rubbing. I am not in favor of oil baths: if there is not too extensive acute skin involvement there is no objection to a water bath twice a week, followed by very careful drying and powdering with plain talc.

Local treatment with salves and lotions varies so much for different individuals and for different types of eruption that it is impossible to discuss it satisfactorily in detail: its principles must be learned by experience. There are certain general rules, however, which should be mentioned. Salves, and lotions containing insoluble powders, are as a rule not desirable during the acute, weeping stage. Wet compresses of 2 per cent resorcin or tannic acid solution containing 2 per cent boric acid, 1 per cent aluminum acetate solution or a 0.05 per cent potassium permanganate solution are better. In most cases of acute dermatitis, such as that caused by poison ivy, after the weeping has been controlled one usually turns to some very mild protective salve, such as Lassar's paste or zinc oxide ointment. For atopic dermatitis in infants, crude-coal-tar ointment may often be used

with advantage at this stage, for the condition is more chronic than is acute contact dermatitis in adults, and there is more thickening. Some of the white-tar preparations on the market are fairly satisfactory, but in my experience none are so good as coal-tar ointment. While the latter is being applied the skin should not be exposed to bright sunlight, and it should never be employed if pyogenic infection is present.

Coal-tar ointment is so efficient in many cases that a tendency has developed among pediatricians to use it on almost all eczematous eruptions. This is a mistake; unless there is considerable thickening and scaling, milder preparations will often do better.

In older children sensitization to environmental allergens is of considerable importance, although it may not often be possible to incriminate any particular allergen. The role of house dust is of some interest, and inasmuch as it is the rule for these patients to improve while in the hospital in a relatively dust-free environment, and to relapse as soon as they go home, and since many of them show large intracutaneous skin reactions to house dust, it probably plays a part, and in not a few cases an important one. If house dust causes dermatitis it probably does so more often by inhalation than by outside contact.

Precautions against dust in the home are as essential for older children with eczema as they are for asthmatic patients. While hyposensitization to house dust has been widely practiced in the treatment of asthma, and is often of benefit, there is little information available to indicate its value in dermatitis, and what information exists is contradictory. The whole subject of desensitization in atopic dermatitis is obscure, and needs additional investigation.

Most older children with eczema have positive skin reactions to a number of foods. Sometimes these are of etiologic significance, sometimes not; this makes difficult a correct evaluation of their presence. Sometimes the dermatitis is caused by a particular food and is cured when it is omitted; perhaps more often several or many foods are omitted without any benefit whatever, and the main cause of the dermatitis may be feathers or house dust, or it may be entirely unknown.

The question of what to omit from the diet, regardless of the skin reaction, is one that requires common sense. The skin tests, to be sure, are helpful, but if one is guided entirely by them and ignores other factors, such as the history and, in particular, careful local treatment, one will have little success. Atopic dermatitis should not be treated without regard to its immunological aspects; nor should it be treated on an immunological basis alone. It must be remembered also that in older children an eruption may have nothing whatever to do with the diet, or with the inhalation of any allergen. It may be due to contact with any one of a wide variety of chemical agents, such as dyes, medicaments and plant oils. Pediatricians in particular are inclined to forget this, because they have always been so interested in food and the digestive tract as the source of numerous ills in children.

There is still a great deal to learn about eczema. There is no sure or quick cure as yet, and to get the better of the disease will require time, patience and much careful investigation.

319 Longwood Avenue

THE PATHOLOGIC PHYSIOLOGY OF BRONCHIAL ASTHMA IN CHILDREN*

With Reference to the Role of Infection

HENRY N. PRATT, M.D.†

BOSTON

THE fundamental pathologic physiology of all atopic and anaphylactic phenomena is increased capillary permeability, smooth-muscle spasm and excessive mucus secretion. These three exaggerations of normal physiologic responses are present in varying degrees in both animals and man. The amount in which any one is active depends on what tissue is involved. For example, in urticaria the primary lesion is increased capillary permeability; in guinea-pig anaphylaxis, smooth-muscle spasm of the bronchioles; and in human hay fever, excessive secretion of mucus associated with increased capillary permeability as evidenced by the pale, edematous nasal mucous membrane. In human allergy there is a fourth

*From the Department of Pediatrics, Harvard Medical School; and the Infants' and Children's Hospitals.

†Instructor in pediatrics, Harvard Medical School; assistant physician, Medical Services, Infants' and Children's Hospitals.

factor, the significance of which is not understood, namely, tissue and sometimes blood eosinophilia.

These four factors can be well demonstrated by examining pathologic tissue from asthmatic children. It is difficult to obtain such material, because death from uncomplicated asthma in childhood is relatively rare. There have been only four cases at the Infants' and Children's Hospitals in the last few years.

Figure 1 shows a gross specimen of lung. It is spongy and fully expanded. Normally the lungs collapse when air is admitted to the pleural cavities, but asthmatic lungs hold their shape and actually remain overextended with air when removed from the chest. Small slices may be cut from the lung, and these too hold their shape instead of collapsing. This is due to two factors. First, the excessive mucoid secretions become dried and inspissated, producing hard, rubbery plugs that completely occlude the bronchioles and smaller bronchi. In the cross section of lung in the illustration this can be readily seen. The mucus plugs tend to stand up beyond the cut surface of the lung. If one grasps a plug with forceps and tries to pull it out, it resists. When released, it snaps back into place. The second factor tending to make the lung hold its shape is spasm of the smooth-muscle coat of the bronchioles. This can be seen in Figure 2. Here will be noted an invagination or wrinkling of the mucous membrane due to spasm of the surrounding smooth-muscle coat. The picture is reminiscent of the anaphylactic guinea-pig lung. This spasm prevents the proper expectoration of the excessive mucus, which consequently dries, producing the plugs. Observation of these specimens explains clearly why the asthmatic child has so much difficulty in breathing during an acute paroxysm.

FIGURE 1. *Cross Section of Asthmatic Lung.*
Note the spongy appearance and the mucus plugs in the bronchi and bronchioles.

Further microscopic studies disclose a mild edema of the peribronchial spaces (Fig. 3). In many of these areas there are excessive numbers of eosinophils. Polymorphonuclear leukocytes are relatively rare, but here and there a group of them may be found, suggesting the presence of some infection, although it is not certain that they necessarily indicate infection. The mucous glands appear hypertrophied and overactive. The plugs of mucus with cellular elements and débris are visible in the lumens of the bronchioles and bronchi. A very characteristic finding is the thickening and hyalinization of the basement membrane of the bronchioles. The significance of this condition is unknown.

The entire pathology in the periphery of the lung is secondary to that in the bronchioles. Em-

physema with flattening and rupture of the alveolar walls is dependent on the ball-valve action of the mucus plugs, which permits the ingress of air during the expansion of the thoracic cavity in inspiration, but traps it behind the plugs during expiration. In other areas there is atelectasis where the mucus plugs have completely occluded the bronchioles, so that the air distal to the plugs is absorbed and the alveolar spaces collapse.

What is the significance of the occasional areas

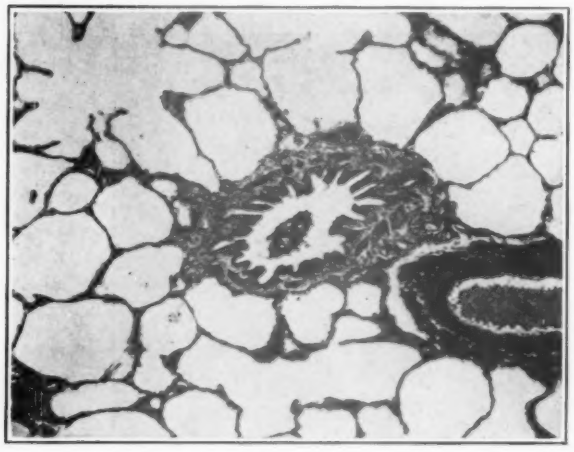


FIGURE 2. *Section of a Constricted Bronchiole.*

Note the resulting flattening and the rupture of the alveolar walls.

of infiltration with polymorphonuclear leukocytes? This brings up the question of infection and its role in the production of an asthmatic attack. At the outset it should be made clear that this question is not yet satisfactorily settled. However, among pediatricians dealing extensively with asthmatic children there is essential agreement.

The part played by infection may be divided into four categories: bacterial allergy; respiratory infections acting as a trigger mechanism; infections secondary to the asthmatic attack; and focal infection. It has often been predicated that a child may become sensitized to bacteria which he harbors somewhere in the respiratory tract. The classic example is pulmonary tuberculosis and the tuberculin reaction. This is certainly an allergic reaction. But asthmatic paroxysms due to sensitivity to the products of the tubercle bacillus are extraordinarily rare. In like manner a delayed, tuberculin-type skin reaction to a bacterium cultured from the respiratory tract of an asthmatic child or to one of its products can often be demonstrated, and undoubtedly means that the child has been infected with that organism. But, just as with tuberculosis, this type of sensitization to an organism is seldom responsible for asthmatic seizures. The occasional satisfactory result following autogenous or stock vaccine therapy is in most cases due to shock and is entirely nonspecific.

Secondly, respiratory infections such as the common cold often precipitate asthmatic attacks in atopic children. In such cases the child is usually sensitive to some food or inhalant which he can tolerate except in the presence of infection. When he catches cold, some alteration occurs in the immunologic mechanism or respiratory mucous membrane so that he can no longer tolerate an extrinsic protein substance to which he is sensitive. This has been clearly demonstrated over and over again by abolishing the extrinsic factor; the child then has a cold without asthma. In these cases the respiratory infection may be considered as a nonspecific trigger mechanism.

Thirdly, infections may be secondary to an attack of asthma initiated by some extrinsic factor

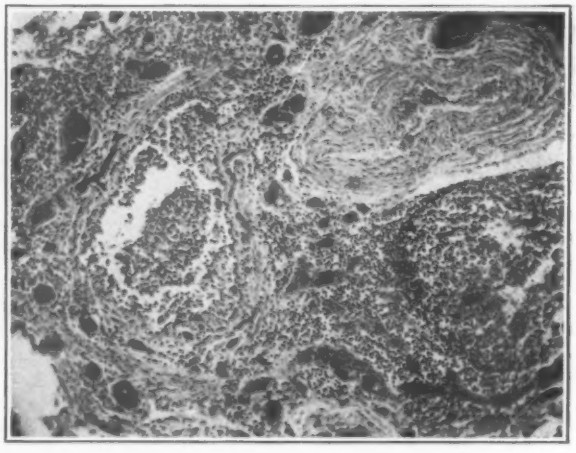


FIGURE 3. *Section of a Bronchiole Filled with a Mucus Plug.*

Note the interstitial edema, the cellular infiltration, consisting mostly of eosinophils, and the hypertrophy of the mucus glands.

to which the child is sensitive. It is a common experience to see a child develop a typical attack of vasomotor rhinitis, often mistaken for a cold. Within a few hours he begins to cough and wheeze. The temperature, however, remains normal, and the pharynx shows no evidence of infection. After twenty-four hours fever and leukocytosis may appear. The infection that is suggested in the microscopic sections by the infiltrations with polymorphonuclear leukocytes probably began in the inadequately aerated portions of the lungs. The infection is entirely secondary. Such infection, once established, may produce a chronic irritation in the bronchi which causes the attacks of asthma to continue intermittently for several weeks. A good example of this is the patient with

ragweed asthma who begins to wheeze in late August when the air is laden with pollen. He is somewhat better in mid-October when the pollen has disappeared, but because of secondary infection he may continue to wheeze until Thanksgiving or even Christmas.

Fourthly, focal infection seldom plays a part in childhood asthma. In allergic children the lymphoid structures in the upper respiratory tract tend to hypertrophy, so that one is sorely tempted to remove the large, boggy tonsils and adenoids. Statistically it has been shown that removal of these structures has no lasting effect on the asthma. If the usual indications for removal of tonsils and adenoids are present, the operation should of course be performed, but asthma is definitely not one of the indications. Essentially the same principles apply in the management of sinuses. If they contain pus, they should be drained, and this sometimes temporarily relieves the asthma, but the presence of pus is rare in the sinuses of asthmatic children. The more usual lesion is a thickened, hypertrophied mucous membrane. This is part and parcel of the allergic reaction, and such sinuses should be left strictly alone so far as operative intervention is concerned.

Summary

The pathology of bronchial asthma is based on the fundamental physiology of atopic and anaphylactic phenomena. Increased capillary permeability produces edema; smooth-muscle spasm of the bronchioles holds the excessive mucus secretions so that they become inspissated and produce tenacious plugs which block partly or completely the smaller bronchi. This results in the formation of areas of emphysema and atelectasis. In the latter sites secondary infection may begin. In general, it may be assumed that infection is a sequela of the asthmatic attack, which is primarily based on an allergic reaction produced by extrinsic causes such as pollens, danders, dusts and foods.

319 Longwood Avenue

THE TREATMENT OF BRONCHIAL ASTHMA IN CHILDREN

ETHAN ALLAN BROWN, M.R.C.S. (LOND.) L.R.C.P.*

BOSTON

THE FACT that bronchial asthma is due to an increased capillary permeability, to smooth-muscle spasm and to excessive mucus secretion has just been stressed. Rational treatment would, of course, direct itself toward the correction of these abnormalities. However, since the cause of the condition is often an extraneous factor such as an inhalant or a food, correction may merely imply complete elimination of the causative allergen.

Treatment is best discussed under the following headings: symptomatic treatment, environmental control and general measures.

The acute attack in children can be treated by any of the sympatheticomimetic drugs of the ephedrine group. Ephedrine sulfate is the best, and the usual dose is 3/8 gr. It has undesirable side actions, and it is necessary that additional sedatives be given. The best of these is undoubtedly phenobarbital, since many of the barbiturates are vasospasmodic. It may be given in doses of ¼ or ½ gr.

For the acute attack of greater severity, small doses of epinephrine (1:1000), 2 or 3 minims, may be injected subcutaneously, and are almost always specific. The dose can be repeated every fifteen minutes for four doses, if necessary. The average dose given is larger than that needed, and very few children require more than 3 minims for relief.

It is not generally known that the oxidation of epinephrine in the system is delayed by the use of ephedrine at the same time. Ephedrine given by mouth will, in cases in which it is not necessarily effective by itself, enhance and prolong the action of the epinephrine.

Other remedies have been used for the acute attack, one of the most popular being syrup of ipecac, which causes nausea and vomiting, and owing to its expectorant action probably relieves the asthmatic spell. It is well to remember that for young children who cannot take a capsule, ephedrine can be put up in syrup form with phenobarbital; also, the capsule can be opened and the contents sprinkled on a teaspoonful of Karo or any other simple, palatable vehicle easily available. I have experimented with suppositories containing ephedrine and phenobarbital. The rectal medication seems effective in children who cannot take it orally.

In the severer cases, epinephrine in oil, 0.5 to 0.8 cc. of the usual preparation (2 mg. per cubic centimeter), should be given every twelve hours, with ephedrine given by mouth at the time of injection and six hours later. Status asthmaticus is not

*Instructor in medicine, Tufts College Medical School; consultant in allergy, Joseph H. Pratt Diagnostic Hospital.

common in children, but when it does occur requires the treatment given to adults. Aminophyllin administered intravenously is used, the dose being 3½ gr.; 50 cc. of 50 per cent sucrose is given at the same time. Epinephrine, 1:1000, may also be given intravenously with this injection, the dose being 0.1 or 0.2 cc. If sucrose is not available, glucose may be employed. Ether in olive oil, 30 cc. of ether to 60 cc. of oil, given rectally will also help to break a severe asthmatic attack. One other drug must be mentioned, if only with a warning against its use. Morphine in any dose and in any form has a deadly effect on an asthmatic child; it should never be used under any circumstances whatsoever. Epinephrine, 1:100, given by inhalation has been utilized, but it is very difficult to teach a child inhalation therapy. Work with animals on the inhalation of epinephrine has shown that it causes local irritation. The possibility that this irritation may itself cause an asthmatic spell by reflex action should not be forgotten.

The symptomatic treatment of the chronic asthmatic child should follow certain definite lines. The classic medication has for years been potassium iodide. It seems to have a mild tonic, expectorant action. It has been given for months at a time, 10 or 20 drops a day, one of the doses being administered at bedtime. I take a very conservative view toward the prolonged treatment of children with harsh remedies. It is, however, possible to make up a mixture of tincture of stramonium, phenobarbital, ephedrine and potassium iodide which, although it seems to be a product of polypharmacy, affords patients with mild chronic asthma prolonged relief. So long as it is realized that such treatment is symptomatic rather than curative, and is to be carried out while all the other studies are being done, no harm will come of such a mixture taken at bedtime over a period of several months.

Usually it does not take the physician very long to discover whether a given case is one of intrinsic or extrinsic asthma. When an inhalant is suspected, environmental control is the most important factor in treatment. I know of a patient with a strong inhalant sensitivity who recovered when taken for an automobile ride. This, of course, is a really dramatic result, and is unfortunately very rare. But, if possible, the removal of the patient to a hospital, although he may not seem very ill at the time, does have an excellent result. This effect is not so marked in the intrinsic type of asthma following an infection, although it must be remembered that the infection may have been a precipitating cause in bringing the extrinsic factor to light. The removal to a good hospital means that the infection will be given adequate continuous care, and that its duration will be shortened considerably.

This is also true in another sense for treatment of the extrinsic type of chronic asthma. Although it is generally admitted that hay fever is due to pollen grains invisible to the naked eye, it is not so easily realized that asthma may be due to dust particles or inhalants in the home, just as often present and in greater amounts, but nevertheless not so apparent. In a child who has a distinct sensitivity to dust, feathers or some other inhalant encountered in the home environment, control must be as complete as possible. It is, of course, apparent that if a patient had, indoors, a collection of flowers to which he was sensitive and got rid of all but one, he would find no relief. It has been found, however, over and over again, that while the removal of every factor but one makes very little difference, the removal of all factors makes a great deal of difference. At the clinic, we sometimes go so far as to have samples of every cushion and every stuffed piece of furniture brought in, and scratch-test the patients with mild alkaline solutions of the substances in order to find exactly which articles are at fault, insisting that these be taken away completely and not merely stored in another room. In this way, we can succeed in curing patients who would otherwise have been ill for a long time.

The environment must also be considered in cases in which small portions of food cause immediate and undeniable symptoms. Children are often given food by well-meaning but ignorant adults. The child, for fear of punishment, may deny having had the food, or may never even be asked, and the mother lists the child's diet without knowing what foods have been taken. For the child whose sensitivity is due to foods acting cumulatively or after a considerable time, food control is more difficult; but here, too, it is possible if the mother is instructed to give only food of known composition. Skin tests are usually of little help in determining food sensitivity, although they may direct suspicion to certain food groups. These sensitivities, however, are more often discovered by elimination diets or by carefully kept food diaries.

Specific treatment by the injection of pollens, inhalants or vaccines is beyond the scope of this discussion.

In asthmatic children, the general care is of paramount importance. This is especially true in the intrinsic cases and in those in which there is a nonallergic family background or an absence of positive skin reactions. A patient who is one of

a large number of children in a family in the low-income group may suffer from continuous infection and almost continuous asthma. In a number of cases, the temporary removal of the patient to a foster home has resulted in his immediate good health. In a home where there are no other children, where the food is good, and where he is given as much attention as he requires, the child no longer has asthma. This improvement is due to the psychologic and physical change in environment. Some children make so great a gain in health that they are able to maintain it on resuming the original environment. Many asthmatic children have been on inadequate diets particularly in regard to vitamins, because of the mother's suspicion that foods have caused the difficulty. I do not wish to seem to advocate "shotgun" vitamin therapy, but unless a child has an adequate vitamin intake, additional vitamin preparations should be given.

The psychological factor is not always vital. But in rare cases it may be the answer to the problem. In the last four years, I have seen at least a dozen cases in which children who were asthmatic used their condition to escape punishment or to acquire privileges and rewards. It is fully as easy for a child as for an adult to employ his bronchial asthma as an escape mechanism or as a method of satisfying his egocentric tendencies. I recall a small boy who refused to be skin-tested. When his mother told him that it would enable him to get well, he stated that he did not want to get well as his mother would then not take him to the country. When the mother said that his health would enable him to go to school, he answered that he was not interested in school. When she said that he would have to go to school nevertheless, he answered that he had plenty of tricks for getting out of school when he wanted to, and that having or not having asthma would not make any difference to him. He presented a behavior problem, and for a child of ten showed a remarkably ingenious mind for using his asthma to achieve anything he wanted. It is, of course, almost impossible to take such spoiled children away from their doting parents, although where the change can be made and the child sent to a camp or school, improvement is usually immediately manifested as ordinary disciplinary rules are enforced. It is, of course, necessary that any other abnormal condition from which the child suffers be corrected.

I am in agreement with what already has been said concerning the tonsils, sinuses and other foci of infection. The tonsils should not be removed from an asthmatic child unless their condition is so bad that their removal is indicated regardless of the asthma. The fact that improvement follows such minor operations is not a sign that the tonsils were the causative factor. The anesthesia, the hospital stay, the operative procedure, the mild temperature, the blood absorption from the open wound (a form of autohemotherapy), may all help to give temporary relief. The allergist too often takes a history in which the patient says that he was well following a tonsillectomy, but that the asthma returned in four or six weeks following this or some other application of surgery.

The health of the patient must be maintained and should be considered continuously, although the asthma may be under control or absent. It has been shown that while allergy is present, although it may be mild, the child's height, weight and intelligence quotient may be abnormal. Attention given to the allergic factors may improve the general condition of the patient although the allergy, as I already said, may not be clinically apparent.

In summary, the mild attack should be treated by an injection of epinephrine subcutaneously in small doses and by ephedrine and phenobarbital administered by mouth. Syrup of ipecac and mild sedatives can be given. In the extrinsic type of case, a change in environment is imperative. In the intrinsic type, any intercurrent infection can be cared for more easily in the hospital than it can be at home. For continuous, chronic asthma, any one of the several remedies containing potassium iodide and tincture of stramonium may be employed. The general care of the child still remains the most vital factor. He should have adequate home care, adequate diet and adequate vitamin therapy; any other abnormalities should, of course, be corrected, but no surgical treatment should be given unless it is demanded in its own right.

Conservative treatment is undoubtedly the key to successful therapy in asthma. Any enthusiasm regarding results should be tempered by the realization that in a good many cases the age factor is important, and that the asthma will probably be outgrown. Although this statement is true and should form part of a balanced point of view, it must be remembered that a child may not outgrow his allergic disease. Adult clinics contain far too many patients with emphysema and deformities in whom treatment was delayed or neglected. The child who receives thorough treatment early in life can almost always be made completely well.

75 Bay State Road

common in children, but when it does occur requires the treatment given to adults. Aminophyllin administered intravenously is used, the dose being 3½ gr.; 50 cc. of 50 per cent sucrose is given at the same time. Epinephrine, 1:1000, may also be given intravenously with this injection, the dose being 0.1 or 0.2 cc. If sucrose is not available, glucose may be employed. Ether in olive oil, 30 cc. of ether to 60 cc. of oil, given rectally will also help to break a severe asthmatic attack. One other drug must be mentioned, if only with a warning against its use. Morphine in any dose and in any form has a deadly effect on an asthmatic child; it should never be used under any circumstances whatsoever. Epinephrine, 1:100, given by inhalation has been utilized, but it is very difficult to teach a child inhalation therapy. Work with animals on the inhalation of epinephrine has shown that it causes local irritation. The possibility that this irritation may itself cause an asthmatic spell by reflex action should not be forgotten.

The symptomatic treatment of the chronic asthmatic child should follow certain definite lines. The classic medication has for years been potassium iodide. It seems to have a mild tonic, expectorant action. It has been given for months at a time, 10 or 20 drops a day, one of the doses being administered at bedtime. I take a very conservative view toward the prolonged treatment of children with harsh remedies. It is, however, possible to make up a mixture of tincture of stramonium, phenobarbital, ephedrine and potassium iodide which, although it seems to be a product of polypharmacy, affords patients with mild chronic asthma prolonged relief. So long as it is realized that such treatment is symptomatic rather than curative, and is to be carried out while all the other studies are being done, no harm will come of such a mixture taken at bedtime over a period of several months.

Usually it does not take the physician very long to discover whether a given case is one of intrinsic or extrinsic asthma. When an inhalant is suspected, environmental control is the most important factor in treatment. I know of a patient with a strong inhalant sensitivity who recovered when taken for an automobile ride. This, of course, is a really dramatic result, and is unfortunately very rare. But, if possible, the removal of the patient to a hospital, although he may not seem very ill at the time, does have an excellent result. This effect is not so marked in the intrinsic type of asthma following an infection, although it must be remembered that the infection may have been a precipitating cause in bringing the extrinsic factor to light. The removal to a good hospital means that the infection will be given adequate continuous care, and that its duration will be shortened considerably.

This is also true in another sense for treatment of the extrinsic type of chronic asthma. Although it is generally admitted that hay fever is due to pollen grains invisible to the naked eye, it is not so easily realized that asthma may be due to dust particles or inhalants in the home, just as often present and in greater amounts, but nevertheless not so apparent. In a child who has a distinct sensitivity to dust, feathers or some other inhalant encountered in the home environment, control must be as complete as possible. It is, of course, apparent that if a patient had, indoors, a collection of flowers to which he was sensitive and got rid of all but one, he would find no relief. It has been found, however, over and over again, that while the removal of every factor but one makes very little difference, the removal of all factors makes a great deal of difference. At the clinic, we sometimes go so far as to have samples of every cushion and every stuffed piece of furniture brought in, and scratch-test the patients with mild alkaline solutions of the substances in order to find exactly which articles are at fault, insisting that these be taken away completely and not merely stored in another room. In this way, we can succeed in curing patients who would otherwise have been ill for a long time.

The environment must also be considered in cases in which small portions of food cause immediate and undeniable symptoms. Children are often given food by well-meaning but ignorant adults. The child, for fear of punishment, may deny having had the food, or may never even be asked, and the mother lists the child's diet without knowing what foods have been taken. For the child whose sensitivity is due to foods acting cumulatively or after a considerable time, food control is more difficult; but here, too, it is possible if the mother is instructed to give only food of known composition. Skin tests are usually of little help in determining food sensitivity, although they may direct suspicion to certain food groups. These sensitivities, however, are more often discovered by elimination diets or by carefully kept food diaries.

Specific treatment by the injection of pollens, inhalants or vaccines is beyond the scope of this discussion.

In asthmatic children, the general care is of paramount importance. This is especially true in the intrinsic cases and in those in which there is a nonallergic family background or an absence of positive skin reactions. A patient who is one of

a large number of children in a family in the low-income group may suffer from continuous infection and almost continuous asthma. In a number of cases, the temporary removal of the patient to a foster home has resulted in his immediate good health. In a home where there are no other children, where the food is good, and where he is given as much attention as he requires, the child no longer has asthma. This improvement is due to the psychologic and physical change in environment. Some children make so great a gain in health that they are able to maintain it on resuming the original environment. Many asthmatic children have been on inadequate diets particularly in regard to vitamins, because of the mother's suspicion that foods have caused the difficulty. I do not wish to seem to advocate "shotgun" vitamin therapy, but unless a child has an adequate vitamin intake, additional vitamin preparations should be given.

The psychological factor is not always vital. But in rare cases it may be the answer to the problem. In the last four years, I have seen at least a dozen cases in which children who were asthmatic used their condition to escape punishment or to acquire privileges and rewards. It is fully as easy for a child as for an adult to employ his bronchial asthma as an escape mechanism or as a method of satisfying his egocentric tendencies. I recall a small boy who refused to be skin-tested. When his mother told him that it would enable him to get well, he stated that he did not want to get well as his mother would then not take him to the country. When the mother said that his health would enable him to go to school, he answered that he was not interested in school. When she said that he would have to go to school nevertheless, he answered that he had plenty of tricks for getting out of school when he wanted to, and that having or not having asthma would not make any difference to him. He presented a behavior problem, and for a child of ten showed a remarkably ingenious mind for using his asthma to achieve anything he wanted. It is, of course, almost impossible to take such spoiled children away from their doting parents, although where the change can be made and the child sent to a camp or school, improvement is usually immediately manifested as ordinary disciplinary rules are enforced. It is, of course, necessary that any other abnormal condition from which the child suffers be corrected.

I am in agreement with what already has been said concerning the tonsils, sinuses and other foci of infection. The tonsils should not be removed from an asthmatic child unless their condition is so bad that their removal is indicated regardless of the asthma. The fact that improvement follows such minor operations is not a sign that the tonsils were the causative factor. The anesthesia, the hospital stay, the operative procedure, the mild temperature, the blood absorption from the open wound (a form of autohemotherapy), may all help to give temporary relief. The allergist too often takes a history in which the patient says that he was well following a tonsillectomy, but that the asthma returned in four or six weeks following this or some other application of surgery.

The health of the patient must be maintained and should be considered continuously, although the asthma may be under control or absent. It has been shown that while allergy is present, although it may be mild, the child's height, weight and intelligence quotient may be abnormal. Attention given to the allergic factors may improve the general condition of the patient although the allergy, as I already said, may not be clinically apparent.

In summary, the mild attack should be treated by an injection of epinephrine subcutaneously in small doses and by ephedrine and phenobarbital administered by mouth. Syrup of ipecac and mild sedatives can be given. In the extrinsic type of case, a change in environment is imperative. In the intrinsic type, any intercurrent infection can be cared for more easily in the hospital than it can be at home. For continuous, chronic asthma, any one of the several remedies containing potassium iodide and tincture of stramonium may be employed. The general care of the child still remains the most vital factor. He should have adequate home care, adequate diet and adequate vitamin therapy; any other abnormalities should, of course, be corrected, but no surgical treatment should be given unless it is demanded in its own right.

Conservative treatment is undoubtedly the key to successful therapy in asthma. Any enthusiasm regarding results should be tempered by the realization that in a good many cases the age factor is important, and that the asthma will probably be outgrown. Although this statement is true and should form part of a balanced point of view, it must be remembered that a child may not outgrow his allergic disease. Adult clinics contain far too many patients with emphysema and deformities in whom treatment was delayed or neglected. The child who receives thorough treatment early in life can almost always be made completely well.

75 Bay State Road

ACUTE HEPATITIS, JAUNDICE AND ABNORMAL BLEEDING AS COMPLICATIONS OF ACUTE APPENDICITIS WITH PERFORATION*

F. A. Simeone, M.D.,† and John D. Stewart, M.D.‡

BOSTON

FATALITIES following operations for acute appendicitis with perforation and peritonitis are usually the result of spreading peritoneal sepsis and its complications. Not uncommonly patients with prolonged intraperitoneal sepsis develop acute hepatitis, which may subside or progress to become a major factor in the patient's death. In these cases, the development of abnormal bleeding is a distressing sign, difficult to control and of grave prognostic significance.

Recent studies (Dam and Glavind[1]; Stewart[2]; Stewart and Rourke[3]) have made progress in describing the nature of the hemorrhagic diathesis associated with jaundice from prolonged obstruction of the extrahepatic biliary passages. It has been shown that in most of these cases the abnormal bleeding is associated with a low plasma-prothrombin level. The evidence indicates that prothrombin is elaborated in the liver by an unknown process involving the participation of the fat-soluble vitamin K. An abnormally low concentration of plasma prothrombin may be due to a failure of vitamin K to reach the liver because of faulty intestinal absorption, as in obstructive jaundice, or to a failure of the damaged liver to elaborate the substance even in the presence of abundant vitamin K. Indeed, some cases of chronic obstructive jaundice present the problem of deficiency not only in absorption but also in liver function, so that both factors are operating to produce a low plasma-prothrombin concentration and the associated bleeding tendency.

The purpose of this report is to discuss two cases of intraperitoneal sepsis complicated by hepatitis and terminal bleeding.

Case 1. J. B. T. (No. 353473), a 17-year-old boy, was admitted to the hospital because of low abdominal pain of 3 days' duration. During the 2 days prior to admission the pain had increased in severity and had become localized. Examination of the abdomen showed generalized tenderness and spasm, with maximal signs in the right lower quadrant. The temperature was 101.0°F. by rectum, the pulse 112, and the respirations 24. The white-cell count was 24,500, and urinalysis showed no abnormality.

Under spinal anesthesia operation was performed for acute appendicitis with perforation. Generalized peritonitis was found and *Escherichia coli* was subsequently cultured from the exudate. The appendix was removed, with drainage of the pelvis and right paravertebral gutter. On the first day after operation progress was satisfactory. Blood chemical studies revealed a hypoproteinemia and some reduction in the alkali reserve. The serum nonprotein nitrogen was 28 mg. per 100 cc., the serum chloride 96 milliequiv. per liter and the carbon dioxide combining power of the serum 35.9 vol. per cent. The serum protein concentration was 4.8 gm. per 100 cc. The patient was given a transfusion of 500 cc. of citrated blood.

On the evening of the 2nd postoperative day, jaundice was first detected in the scleras and bile was noted in the urine. By the following day the jaundice had deepened and a serum van den Bergh test showed a direct reaction, with 11.1 mg. of bilirubin per 100 cc. There had been no chills. The patient then showed clinical improvement and the jaundice began to clear, until by the 5th postoperative day the serum bilirubin was 6.5 mg. The temperature had fallen to normal. The next day, however, there was an abrupt rise in temperature to 103.2°F. by rectum, and from then on the patient's course was progressively downhill. The jaundice deepened again, until by the 9th postoperative day the bilirubin in the serum had risen to 12.6 mg. The same day there was bleeding from the wound amounting to about 300 cc. The bleeding continued the next day in spite of transfusions, the abdomen grew increasingly distended, and the patient became disorientated and delirious. A hematoma in the right paravertebral gutter was drained under local novocain anesthesia on the 10th postoperative day. Two days later the serum nonprotein nitrogen rose to 43 mg. per 100 cc., and the bilirubin to 21.4 mg. The patient died the next day, 13 days after operation. There had been some decrease in the bleeding from the wounds, but not complete cessation.

The significant abdominal findings at postmortem examination were generalized peritonitis and diffuse central necrosis of the liver. In addition there were found acute fibrinous pericarditis, acute pleuritis with pyohydrothorax, and *Esch. coli* and *Streptococcus faecalis* bacteremia. Jaundice was quite obvious at autopsy and was attributed to the hepatitis. The infected hematoma was found to have been well drained, but there was residual retroperitoneal sepsis, and the exudate was peculiarly hemorrhagic in character.

Case 2. A. I. (No. 188575), a 13-year-old girl, was admitted to the hospital for treatment of acute appendicitis with perforation and spreading peritonitis. The temperature was 101.8°F. by rectum, the pulse 112, and the respirations 24. The white-cell count was 32,000, with 81 per cent polymorphonuclears, of which 5 per cent were "stab" forms. The urine was normal. Under ether anesthesia a gangrenous perforated appendix was removed through a right pararectus incision. The pelvis was drained by a cigarette wick through a stab wound in the right flank.

*From the Surgical Laboratories of the Harvard Medical School at the Massachusetts General Hospital.

†Instructor in genitourinary surgery, Harvard Medical School; fellow in urology, Peter Bent Brigham Hospital.

‡Associate in surgery, Harvard Medical School; assistant surgeon, Massachusetts General Hospital.

There was no evidence of localization of the peritonitis. Cultures of the exudate showed *Esch. coli, Proteus vulgaris* and nonhemolytic streptococci.

Postoperatively the patient showed steady improvement until the 8th day, when after a brief, mild chill the rectal temperature suddenly rose to 105°F. There was a corresponding rise in the pulse and respirations. In the evening a trace of jaundice became detectable in the skin and scleras. Twelve hours later the serum bilirubin concentration was 4.9 mg. per 100 cc. This increased the next day, 10 days after operation, to 5.9 mg. The reaction was biphasic.

An indwelling stomach tube was kept on constant suction, and an adequate fluid balance was maintained by means of venoclyses and transfusions. The jaundice temporarily decreased, although the patient's condition continued to fail. On the 13th postoperative day, bleeding from the appendectomy wound set in. There was a generalized oozing from the superficial granulations as well as from the depths of the wound. Packing was only partly successful in controlling the bleeding. Four transfusions, totaling 2000 cc. of citrated blood, were given during the next 2 days, without appreciable effect on the bleeding tendency. Fifteen days after operation the plasma prothrombin concentration was down to 38 per cent of normal. Capsules of vitamin K and bile acids were given orally. During the same day, however, the patient began to have convulsive attacks, became comatose and died. Before death the serum nonprotein nitrogen had increased to 38 mg. per 100 cc. The chlorides were 104.8 milliequiv. per liter, and the serum-protein concentration 5.2 gm. per 100 cc. The van den Bergh reaction was still biphasic, and the serum bilirubin concentration was 13.1 mg. Autopsy was not performed.

The postoperative courses in these cases showed remarkable general similarities. Both patients had generalized peritonitis secondary to a ruptured acutely inflamed appendix. Each showed initial improvement after operation, followed by relapse. Jaundice was observed early in Case 1, late in Case 2. Of particular interest is the fact that both patients terminally developed a hemorrhagic diathesis.

The jaundice in Case 1 was attributable to liver insufficiency. Although objective evidence is lacking in Case 2, the clinical course was so similar to that of Case 1 that it is reasonable to assume a similar cause for the jaundice. Plasma-prothrombin studies were not done in Case 1, as the determination was not then clinically available. In Case 2, a severe hypoprothrombinemia was found (38 per cent of normal), and again it is reasonable to attribute the abnormal bleeding of Case 1 to a similar deficiency in plasma prothrombin.

Ample evidence has accumulated since Dam[4] demonstrated a relation between abnormal bleeding and fat-soluble vitamin deficiency, indicating that a failure in the absorption or utilization of vitamin K is responsible for the hemorrhagic diathesis in patients with obstructive jaundice. Such patients have been found to have an abnormally low concentration of prothrombin in the plasma, with resultant inadequacy of the clotting mechanism. Just what part is played by vitamin K in the synthesis or activation of prothrombin is not known.

In the 2 cases described above, the abnormal bleeding was probably due to a disorder in the vitamin K content. Three possible explanations present themselves:

The postoperative diet may have been deficient in vitamin K. If this were the vital factor, however, it would seem that the deficiency would become apparent more frequently in surgical practice.

The absorption of vitamin K from the intestinal tract may have been impaired. In obstructive jaundice the impairment is due to lack of bile salts in the gastrointestinal tract, with a consequent decrease in the absorption of fat-soluble substances. In general peritonitis, the decreased absorption might be due to the frequently associated enteritis.

The disturbed liver functions attending the hepatitis may have interfered with the normal reaction whereby vitamin K effects the liberation or activation of prothrombin in the liver.

The last of the above suggestions appears to be the most plausible. It fits with the report of Greaves and Schmidt,[5] who found that in rats deficient in vitamin A, even though carotene was supplied in abundance parenterally, there was no evidence that vitamin A was elaborated in the presence of liver damage. It follows from this interpretation that in cases of abnormal bleeding, such as the two presented above, oral or parenteral administration of vitamin K is not nearly so effective as it is in those cases where the fault is primarily one of intestinal absorption rather than depression of liver function. In this group, vitamin K therapy should be actively supplemented by transfusion.

Summary

Two cases are described to illustrate the syndrome of acute hepatitis and hypoprothrombinemic bleeding following operation for acute appendicitis with perforation. Such bleeding may result in serious blood loss and extension of infection. Plasma prothrombin concentrations should be determined in cases of peritoneal infection of gastrointestinal origin, and blood transfusions and parenteral vitamin K therapy should be given as indicated.

REFERENCES

1. Dam, H., and Glavind, J.: The clotting power of human and mammalian blood in relation to vitamin K. *Acta med. Scandinav.* 96:108-128, 1938.
2. Stewart, J. D.: Prothrombin deficiency and the effects of vitamin K in obstructive jaundice and biliary fistula. *Ann. Surg.* 109:588-595, 1939.
3. Stewart, J. D., and Rourke, G. M.: Control of prothrombin deficiency in obstructive jaundice by the use of vitamin K. *J. A. M. A.* 113:2223-2227, 1939.
4. Dam, H.: The antihaemorrhagic vitamin of the chick: occurrence and chemical nature. *Nature* 135:652, 1935.
5. Greaves, J. D., and Schmidt, C. L. A.: The utilization of carotene by jaundiced and phosphorus treated vitamin A deficient rats. *Am. J. Physiol.* 111:502-506, 1935.

REPORT ON MEDICAL PROGRESS

ORTHOPEDIC SURGERY

JOSEPH S. BARR, M.D.*

BOSTON

ALTHOUGH disabilities of the musculoskeletal mechanism have been recognized and treated since the earliest times, it is only in recent years that orthopedic surgery has been recognized as a specialty. Its growth has been phenomenal. The recent report[1] of the Research Committee of the American Orthopaedic Association gives some indication of the number, variety and scope of the various research projects being carried on throughout the United States.

Perhaps one of the most characteristic features of the specialty is the fact that operative procedures are not well standardized; for the relief of an orthopedic disability by operative means, there is usually more than one choice, and sometimes an embarrassingly large number of operative procedures from which the surgeon must choose. Textbooks on surgical technic become outmoded very rapidly, but two recent books[2, 3] on operative orthopedics are so well written and illustrated that they should prove invaluable to the general surgeon in selecting the proper operation for a given case.

INEQUALITY IN LEG LENGTH

A wide variety of conditions, congenital or acquired, affect epiphyseal growth and cause discrepancy in leg length. If the discrepancy is less than 5 cm., it can be compensated for by a raise on the heel of the shoe, but more than that amount requires an unsightly high sole. Equalization of leg length up to 5 to 8 cm. can be produced by leg-lengthening procedures. The most popular and effective of these is the one described by Abbott,[4] in which after osteotomy of the tibia and fibula and lengthening of the tendo achillis, the bone fragments are gradually distracted by means of skeletal traction. This entails prolonged hospitalization and a certain amount of risk of delayed or nonunion, sepsis, malalignment, joint disabilities and so forth; and although it still holds a place in the armamentarium of orthopedic surgery, it is definitely less popular than it was a few years ago. Leg-shortening procedures, in which the sound limb is operated on, sacrificing a predetermined amount of length of the femur, have become more popular in recent years and seem to be supplanting the lengthening procedures as the method of choice in adults.[5] Growing children who have progressively increasing shortening of one leg may be treated by sympathectomy (lumbar ganglionectomy) in an attempt to stimulate epiphyseal growth by increasing the peripheral circulation of the extremity. This procedure seems to be particularly effective in cases of poliomyelitis, but it must be done before much shortening has occurred.

Epiphyseal arrest (epiphyseodesis) has been proposed by Phemister.[6] It seems to be the best method thus far devised for equalization of leg length in children. The principle of the operation is simple. By placing bone grafts across one or more growing epiphyses of the longer leg, a premature union of the epiphysis and diaphysis is brought about, and the final leg length is less than it would normally have been. The epiphyses at the knee joint, particularly the femoral epiphysis, are most commonly used. The choice of time of operation and the number of epiphyses to be fused depends on a number of variable factors, too involved to be discussed here. The important point is that there are now effective methods for the equalization of leg length, and that every child with appreciable discrepancy in rate of growth of the lower extremities should be under the observation of a competent orthopedic surgeon.

ARTHROPLASTY

One of the most interesting and spectacular procedures of the orthopedic surgeon is the re-

*Instructor in orthopedic surgery, Harvard Medical School; assistant visiting orthopedic surgeon, Massachusetts General Hospital.

establishment of motion in ankylosed joints. Successful results have been recorded for years, particularly in the knee, hip and elbow. Most surgeons have relied on the interposition of a double layer of fascia lata between the newly formed joint surfaces. Although fascia-lata arthroplasty of the elbow and knee is successful in a fairly high percentage of cases, the procedure as applied to the hip has not become very popular because of the rather high incidence of re-ankylosis or of painful joints after the operation. Smith–Petersen[7] after years of experimentation with various types of molds interposed between the acetabulum and the head of the femur has finally evolved a technic for arthroplasty of the hip which seems to give satisfactory results in a high percentage of cases. A vitallium cup is fitted loosely over the head of the femur. This metal seems to cause little or no tissue reaction and, apparently, may be left in situ for an indefinite period of time, allowing free gliding motion of the bony surfaces on either side of the cup. Careful selection of the operative cases, proper operative technic and meticulous attention to postoperative care are all still essential if successful results are to be obtained. Attempts are being made to use this same material in arthroplasties of other joints, and it is to be anticipated that a suitable technic may be evolved for various joints of the body.

Nonabsorbable Fixation Material

The trend toward the use of nonabsorbable suture material, particularly silk, in clean surgical cases is as pronounced in orthopedic surgery as it is in other branches of surgery. The incidence of postoperative infection seems to be definitely decreased, and better and stronger wound healing seems to occur where proper silk material is substituted for absorbable catgut sutures.

Within the last few years, two new nonabsorbable fixation materials have proved themselves to be of real aid to the orthopedic surgeon. Stainless steel in the form of bone plates, screws, Steinmann pins, Kirschner wires and flexible suture wire has practically displaced the previously used vanadium steel. The more recently introduced vitallium,[8] an alloy of cobalt, molybdenum and chromium, containing no iron, has also become very popular. Its one drawback seems to be that it is not malleable and is made by casting, so that there is some tendency toward brittleness. Both these materials seem to be practically inert, causing no irritation of the body tissues, even when left in place over long periods of time.

Low-Back Pain and Sciatica

Low-back disability continues to be one of the most important and difficult problems confronting the orthopedic surgeon. Recent medical literature contains many articles concerning various aspects of this question. Under the intensive study which is now being carried out, new concepts of the etiologic factors involved are being elucidated, and it is fair to say that real progress is being made in the diagnosis and treatment of low-back disability. It needs to be reiterated and emphasized that a long list of etiologic possibilities are present in any given case, and that the solution of the problem depends on the taking of a detailed history, which includes not only the details of the present disability but also an investigation of the past history and the general medical and social factors. The physical examination must include a general medical examination and a detailed examination of the back in the standing, sitting and lying positions. Various special diagnostic tests[9] are a necessary part of this examination. Also necessary is a routine neurological check-up, which should include at least eliciting the usual reflex responses, a check on the superficial and deep sensory responses to appropriate stimuli and an estimate of the muscular strength in the lower extremities and trunk. With this information at hand, the physician can select the necessary x-ray and laboratory examinations, and when their results are known, can synthesize a working diagnosis and outline suitable therapy in the great majority of cases. The day when a pain in the back was usually referred to as "slipped sacroiliac" has drawn to a close.

Steindler[10, 11] has pointed out that for clinical purposes it is useful to divide the factors responsible for low-back and sciatic pain into two major groups. In the first, the disability is due to direct pressure within the spinal canal on the sciatic nerve, the lumbar plexus or the cauda equina. This may be caused by tumor, protruded intervertebral disk, hypertrophied ligamentum flavum and so forth. The symptoms in the second group are due to strain or irritation of a "trigger point" in the low back, with secondary reflex sciatic radiation of the pain. In this group there is no direct pressure on or irritation of the sciatic nerve or its components within the spinal canal. The diagnosis depends on finding a point of local tenderness, on which pressure accentuates the reflex referred pain, and its release at least partial relief from the pain. Local infiltration of the tender area with novocain produces complete temporary abol-

ishment of the reflex pain, and in some cases brings permanent cure. Examination of Steindler's cases of reflex sciatica reveals that they fell into six major groups: the sacrospinalis syndrome, in which the tender area was localized in the region of the posterosuperior or posteroinferior iliac spine; the lumbosacral syndrome, in which the point of tenderness was in the midline at the lumbosacral junction or over the fifth lumbar spinous process; the gluteal syndrome, in which the tenderness was lateral to the posteroinferior spine in the region of the origin of the gluteus maximus muscle; the transversosacral syndrome, in which tenderness was found in the iliolumbar angle and was associated with sacralization of the fifth lumbar transverse process; the tensor-fascia-lata syndrome, in which the Ober[12] test was positive and there was tenderness over the fascia lata, usually between the iliac crest and the great trochanter; and the myofascial syndrome, in which the tenderness was not well localized, but was usually present over the erector spinae muscle groups on either side of the spinous processes of the lumbar vertebrae.

Anatomic variations in the formation of the lumbosacral skeleton are common, and in the past certain of these have been considered to be common causes of low-back and sciatic pain. The consensus at the present time seems to be that no one of these variations is inevitably followed by back disability, and that in many cases their presence as revealed by the x-ray is an incidental finding.

Spondylolisthesis, or forward displacement of the vertebral column consequent to a defect or solution in continuity in the neural arch of a vertebra, is present in 5 or 6 per cent of the general population. However, examination of 200 fetal skeletons failed to reveal a single case of this condition, and for this reason Batts[13] thinks that the congenital-malformation theory is untenable. Hitchcock[14] in a careful study of the vertebral ossification centers of 90 fetal spines also failed to find a single example of spondylolisthesis or of accessory ossification centers. He noted, as has Willis,[15] the presence of an area of great potential weakness at the isthmic zone, and was able experimentally to produce fractures in this area with very little force by hyperflexion of the spine. He concludes that spondylolisthesis is due to birth trauma and is not a congenital anomaly. Recurrent or persistent lumbosacral backache, sometimes accompanied by radiation of pain down the posterior thighs, is the commonest symptomatology associated with spondylolisthesis, although Friberg[16] found that 10 per cent of his patients had no symptoms whatever, and that many of them were able to do heavy work. There are two available methods of treatment of this condition. The conservative method includes some type of support, such as a corset or brace, restriction of activities to within the limits of discomfort, and carefully graded exercises. If this procedure fails to relieve symptoms, or if there is evidence of increased displacement of the vertebra, operative fusion of the area is indicated.

Ruptured Intervertebral Disks and Thickening of the Ligamentum Flavum

In 1934 a paper was published by Mixter and Barr[17] in which attention was called to the fact that posterior protrusion of intervertebral-disk tissue into the spinal canal occurred more frequently than had previously been supposed, and that the symptoms in such cases were often similar to those attributed to sacroiliac strain, that is, acute low-back pain accompanied by severe sciatic radiation. Interest in this subject has increased from year to year, and there have been several recent symposiums.[18, 19] It now seems quite definitely established that one of the commonest, if not the commonest, causes of intractable sciatic radiation of pain unrelieved by the usual supportive measures is posterior protrusion of an intervertebral disk in the low-lumbar region pressing on one or more roots of the cauda equina. Although both sexes and almost all ages are affected, by far the majority of cases occur in vigorous men between the ages of twenty and forty-five. A history of an injury to the back while lifting a heavy weight or of a fall from a height is elicited in about half the cases. There may be a long history of relapses and remissions, with a final attack which is severe and unrelieved by any of the usual conservative methods of treatment. The pain characteristically radiates down the posterior thigh and the posterolateral calf to the ankle. On examination, abnormal flattening or actual reversal of the lumbar lordosis is noted, often with a list of the lumbar spine either toward or away from the affected side. All motions of the lumbar spine are restricted by muscle spasm, and there may be a point of local tenderness in the midline at the lumbosacral junction or just above it. Straight leg-raising on the affected side is as a rule markedly limited. Jugular compression may cause exacerbation of the radiating pain. A diminished or absent ankle jerk is the commonest neurologic finding. In addition, there may be areas of diminished sensation or anesthesia, usually of the lateral border of the foot or the outer aspect of the calf of the leg. In a few cases the lesion is so large as

to cause symptoms of paraplegia. The protein content of the cerebrospinal fluid is usually elevated, but a small percentage of cases give perfectly normal cerebrospinal-fluid findings. Routine x-ray examination may reveal some narrowing of the fourth or fifth lumbar intervertebral disk, but an absolute localization and diagnosis of this lesion cannot be made except by roentgenologic examination after the injection of a contrast medium. The use of air or oxygen (pneumomyelography) has been advocated by Chamberlain.[20] Other roentgenologists, particularly Camp[21] and Hampton,[22] have advocated Lipiodol. An accurate localizing diagnosis can be made with Lipiodol in over 90 per cent of cases, but the use of this contrast medium is not without some hazard, and it should be reserved for those cases in which the diagnosis cannot be made otherwise and in which surgery is necessary, so that the Lipiodol can be removed at the time of the laminectomy.

The treatment of ruptured intervertebral disk consists in laminectomy and removal of the extruded fragments. This gives relief of symptoms, often in a very dramatic fashion, in about 90 per cent of cases. The final results seem to be somewhat better if the operative area is strengthened by a spine fusion done at the same time the laminectomy is performed.

It has been demonstrated by Schmorl[23] and more recently by Horwitz[24] that posterior intervertebral-disk protrusions can be demonstrated by routine autopsy examination in a fairly high percentage of cases, apparently never having caused clinical symptoms. There is also a good deal of evidence to show that the acute symptoms of a certain percentage of the clinical cases may subside or disappear completely under conservative treatment. The most effective method of conservative treatment seems to be immobilization of the lumbar spine in a plaster cast, applied with the lumbar spine in a position of flexion. If this fails to give relief within a few weeks, operative removal of the protruded disk should be undertaken.

Thickening of the ligamentum flavum as the cause of low-back and sciatic pain has been mentioned in a previous progress report.[25] It is much less common than protrusion of the intervertebral disk, and the two lesions may occasionally be associated. The symptoms and signs of the two entities are very similar.

234 Marlboro Street

References

1. Research Committee of the American Orthopaedic Association: Orthopedic research in North America. *J. Bone & Joint Surg.* **22**:752-758, 1940.
2. Steindler, A.: *Orthopedic Operations: Indications, technique and end results.* 766 pp. Springfield, Illinois: Charles C Thomas, 1940.
3. Campbell, W. C.: *Operative Orthopedics.* 1154 pp. St. Louis: C. V. Mosby Co., 1939.
4. Abbott, L. C., and Saunders, J. B.: Operative lengthening of the tibia and fibula. Preliminary report on further development of principles and technic. *Ann. Surg.* **110**:961-991, 1939.
5. Wilson, P. D., and Thompson, T. C.: A clinical consideration of the methods of equalizing leg length. *Ann. Surg.* **110**:992-1015, 1939.
6. Phemister, D. B.: Operative arrestment of longitudinal growth of bones in the treatment of deformities. *J. Bone & Joint Surg.* **15**:1-15, 1933.
7. Smith-Petersen, M. N.: Arthroplasty of the hip: new method. *J. Bone & Joint Surg.* **21**:269-288, 1939.
8. Venable, C. S., and Stuck, W. G.: Vitallium nails in fractures of the hip. *Surg., Gynec. & Obst.* **70**:964-968, 1940.
9. Ellis, J. D.: Examination of the injured back. *Am. J. Surg.* **42**:561-576, 1938.
10. Steindler, A.: Differential diagnosis of pain low in the back: allocation of the source of pain by the procaine hydrochloride method. *J. A. M. A.* **110**:106-113, 1938.
11. *Idem:* The interpretation of sciatic radiation and the syndrome of low-back pain. *J. Bone & Joint Surg.* **22**:28-34, 1940.
12. Ober, F. R.: Relation of the fascia lata to mechanical disabilities of the spine. *Surgery* **4**:21-32, 1938.
13. Batts, M.: The etiology of spondylolisthesis. *J. Bone & Joint Surg.* **21**:879-884, 1939.
14. Hitchcock, H. H.: Spondylolisthesis: observations on its development, progression, and genesis. *J. Bone & Joint Surg.* **22**:1-16, 1940.
15. Willis, T. A.: The separate neural arch. *J. Bone & Joint Surg.* **13**:709-721, 1931.
16. Friberg, S.: Studies on spondylolisthesis. *Acta chir. Scandinav.* Supp. **55**:1-140, 1939.
17. Mixter, W. J., and Barr, J. S.: Rupture of the intervertebral disc with involvement of the spinal canal. *New Eng. J. Med.* **211**:210-215, 1934.
18. Walsh, M. N.: Clinical and neurological aspects of low back and sciatic pain. *Radiology* **33**:681-687, 1939.
19. Love, J. G.; Spurling, R. G.; Grantham, E. G.; Saunders, J. B.; Inman, V. T.; Stookey, B.; Macey, H. B.; Hampton, A. O.; Walsh, M. N.; Galloway, J. D. B.; Broders, A. C., and Ghormley, R. K.: Symposium of protruded intervertebral disks. *Arch. Surg.* **40**:373-538, 1940. Barr, J. S.; Smith, A. DeF.; Ober, F. R., and Mitchell, J. I.: Symposium on low back pain. *Surgery* **4**:1-43, 1938.
20. Chamberlain, W. E., and Young, B. R.: The diagnosis of intervertebral disk protrusion by intraspinal injection of air: air myelography. *J. A. M. A.* **113**:2022-2024, 1939.
21. Camp, J. D.: The roentgenologic diagnosis of intraspinal protrusion of intervertebral disks by means of radiopaque oil. *J. A. M. A.* **113**:2024-2029, 1939.
22. Hampton, A. O., and Robinson, J. M.: The roentgenographic demonstration of rupture of the intervertebral disc into the spinal canal after the injection of lipiodol. *Am. J. Roentgenol.* **36**:782-803, 1936.
23. Schmorl, G.: Ueber Knorpelknoten an der Hinterfläche der Wirbelbandscheiben. *Fortschr. a. d. Geb. Röntgenstrahlen.* **40**:629-634, 1929.
24. Horwitz, T.: Lesions of the intervertebral disc and ligamentum flavum of the lumbar vertebrae: an anatomic study of seventy-five human cadavers. *Surgery* **6**:410-425, 1939.
25. Ayer, J. B.: Report on medical progress: clinical neurology. *New Eng. J. Med.* **223**:376-380, 1940.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 26421

PRESENTATION OF CASE

A sixty-two-year-old physician entered the hospital complaining of increasing dyspnea and edema of three and a half months' duration.

The patient stated that his systolic blood pressure had been between 160 and 170 for many years and that he had had an occasional twinge of apical non-radiating cardiac pain, lasting but a few minutes and usually brought on by emotion. Five years before admission he had an acute attack of severe precordial pain, and an electrocardiogram at that time indicated a posterior occlusion. He remained in bed for one month thereafter and then returned to work, with no untoward effects until one year before entry. At that time he exerted himself unduly, and this indiscretion was followed by marked dyspnea, cough and bloody sputum. These symptoms all cleared with rest. Nine months before admission he was digitalized, put on a maintenance dose of 0.1 gm. daily and carried on until four months before entry, when he noticed the gradual onset of increasing nausea, anorexia and dyspnea. One month before admission the digitalis was discontinued in a partially successful attempt to control the nausea, with the result that peripheral edema developed and dyspnea finally prevented him from lying down.

His past illnesses and family history were irrelevant.

Physical examination showed a sallow, dyspneic, man who coughed frequently and complained of pain in the right chest. The neck veins were pulsating slightly. The heart borders were percussed 3 cm. from the midline on the right and 11 cm. on the left; the supracardiac dullness was 6 cm. in breadth. The rate was rapid, with a gallop rhythm and an auscultatory pulsus alternans at 118 to 130 systolic, 80 diastolic. In addition there was a high-pitched murmur, which was thought to be diastolic but which was impossible to time accurately because of the rapid heart rate. The lung bases were dull to percussion, with moist rales and distant breath sounds on auscultation. There was also a slight right axillary friction rub. The tender liver was palpated two fingerbreadths below the costal margin, and there was an abdominal fluid wave and shifting dullness. There was pitting edema of the legs, extending up to the midthighs, and in the sacral region.

The temperature was 100.4°F., the pulse 120, and the respirations 28.

Examination of the urine was negative. The blood showed a red-cell count of 4,700,000 with a hemoglobin of 85 per cent, and a white-cell count of 27,400 with 90 per cent polymorphonuclears. The nonprotein nitrogen of the blood was 58 mg. per 100 cc.

The patient was treated with digitalis and diuretics, but at no time did he respond favorably, although his peripheral edema decreased. Three weeks after admission, his temperature rose abruptly and he coughed up bloody sputum. He gradually became disorientated, developed a pleuropericardial friction rub and died one month after admission.

DIFFERENTIAL DIAGNOSIS

DR. SYLVESTER MCGINN: If we have all the information available on this patient,—and I assume that we have,—we should be able to make an adequate diagnosis. The first clue to possible etiology of the illness is the story of a systolic blood pressure of 160 to 170 for years. The corresponding diastolic pressures are not mentioned, and the only complete reading noted was 118 to 130 systolic, 80 diastolic. Because the blood pressure was obtained when the patient was critically ill and in failure, we cannot say much about it. I think the systolic pressures of 160 to 170 do bring in a certain hypertensive factor. The next possible etiological clue is the story of occasional twinges of an apical, non-radiating cardiac pain, which came on with emotion and which lasted only a few minutes. This history alone does not justify a diagnosis of angina, but fortunately we can confirm involvement of the coronary vessels from the next sentence, which states that there was an acute attack of severe chest pain and electrocardiographic evidence of posterior coronary occlusion. That is definite. No other evidence brought into the abstract suggests any further coronary attacks. Yet if this man had one right coronary occlusion five years before he died, I should not be surprised if at postmortem he showed additional coronary involvement. It is impossible to localize it as to time.

It is interesting that the patient lived for five years with cardiac infarction and was an active physician, and that only one year before death did congestive failure begin to appear, although he

had apparently taken only one month's rest after the acute coronary attack. The symptoms of cardiac failure — shortness of breath, cough and bloody sputum — sound like more than paroxysmal attacks of cardiac asthma, for the description does not suggest that they were paroxysms with asthmatic wheezes coming at night. Moreover, it seems a farther advanced process — pulmonary edema with bloody sputum. These symptoms all cleared with rest. That brings up an important point in the treatment of this case. The patient was digitalized and put on a maintenance dosage, but no reference is made as to whether he also had diuretics at that time; it is just as important to treat early signs of left ventricular failure with diuretics as it is to use them later, when there is evidence of peripheral edema and anasarca. I think perhaps it is even more important, because you can hope to accomplish more with them and keep the patients free from symptoms of cardiac asthma for some time. As a matter of fact, in the cases of cardiac asthma looked up here, the average duration of life, once it appeared, was 1.6 years. In another series the average duration of life was 2.4 years. I believe that in the latter the improvement was due to the use of diuretics in addition to digitalis.

The digitalis was omitted in a partially successful attempt to control nausea and anorexia. The patient had been having increased dyspnea, and I suspect that a good part of the anorexia and nausea was due to increased congestion, rather than being dependent solely on the use of digitalis. Anorexia, nausea and all gastric disturbances are extremely common symptoms of congestion in any cardiac case.

The next thing leading to a diagnosis is the pain in the right chest, and later on we find that the patient had a moderate right axillary friction rub. It makes little difference whether it was slight or not; it was a definite finding, and I think the most logical explanation is pulmonary infarction. In the terminal illness there is another reference to a pleuropericardial rub, which may have been evidence of a pulmonary infarct on the other side. If you have one embolus the chances are that you are going to have another. The patient had a temperature of 100.4°F. This is important because Drs. Kinsey and White* have pointed out that any time a patient with congestive failure has an increase in temperature there should be some reason for it, and that the commonest cause of febrile reaction in congestive failure is pulmonary infarction.

The neck veins were pulsating slightly, a finding which is consistent with failure of the right ventricle. There was evidence of increase in heart size, with the left border 11 cm. from the midline, and also gallop rhythm and auscultatory pulsus alternans. Pulsus alternans and gallop rhythm indicate left ventricular dilatation, and imply a very serious prognosis. One cannot say much about the high-pitched murmur that was impossible to time because of a rapid heart rate. It is not fair to make the diagnosis of valvular deformity on that description alone. In congestive failure with dilatation, it is not uncommon to hear systolic murmurs, oftentimes due to distention and dilatation of the mitral ring. I believe that if it was the systolic murmur of aortic stenosis the description would be more definite. The patient had evidence of right-sided heart failure — pitting edema to the thighs, ascites and a palpable liver. In other words he had left ventricular failure, followed by evidence of right-sided failure.

Examination of the urine was negative. Yet we later have the finding of a nonprotein nitrogen of 58 mg. per 100 cc., which I believe was probably due to the congestion. If there had been any considerable nephritic damage, the patient would not have had a normal urine. The white-cell count of 27,400 is high for uncomplicated pulmonary infarction, and rather high for phlebitis. There is no evidence of where the emboli originated. Often in cardiac cases we never do find where they started. They did not come from an intramural thrombus, because the only evidence of an acute coronary occlusion had occurred five years previously. I believe the congested veins became thrombosed at some point, as they very frequently do.

The terminal illness is not unusual, and yet it is of some interest. In spite of active treatment, — digitalis and diuretics, — the failure increased; this means that the heart muscle was beyond the point of being helped by rest or treatment. It is a fact, too, that when we do find pulmonary infarction in cardiac cases they are very resistant to digitalis or any other kind of therapy. Three weeks after admission and one week before death, the patient's temperature rose abruptly, and he coughed up bloody sputum. The sudden rise in temperature may have meant further infarction, or a pneumonic process. He became disorientated and developed a pleuropericardial friction rub. Were there any other determinations of the nonprotein nitrogen?

DR. HOWARD B. SPRAGUE: The nonprotein nitrogen was 22 mg. per 100 cc. on admission.

DR. MCGINN: Do you know when it changed to 58 mg.?

DR. SPRAGUE: A week before he died.

DR. MCGINN: He was admitted with a non-

*Kinsey, D., and White, P. D.: Fever in congestive heart failure. *Arch. Int. Med.* 65:163-170, 1940.

protein nitrogen of 22 mg., which later rose to 58 mg.; I presume the increase was dependent on the increasing congestion, because he apparently came in with properly functioning kidneys. The pericardial rub was probably not uremic in origin.

To make a final diagnosis, I am not sure of the hypertensive factor, but everything seems to fit in with it, especially the heart size and the story of an elevated systolic pressure. I should like to make a diagnosis of hypertensive arteriosclerotic heart disease, with an old posterior coronary occlusion, — there may have been other evidence of coronary disease, but this was the only definite occlusion, — cardiac hypertrophy and dilatation, especially of the left ventricle, congestive heart failure, first left-sided and later right-sided, multiple pulmonary infarction and terminal bronchopneumonia.

Dr. Sprague: The patient was taken care of by one of his confreres. I saw him in consultation several times, but he managed most of his own therapy. He was a very apprehensive individual, who gave up a good deal of his practice after he had had the cardiac infarct, but I was impressed at each examination how abnormal his heart remained, with poor sounds and with persistent gallop rhythm. Fluoroscopically the heart was apparently generally dilated and the pulsations were poor. He took digitalis, became nauseated, failed increasingly, omitted the digitalis and got into a vicious circle so that it was necessary to give diuretics. His physician preferred to have him in the hospital here. The diagnosis made was the one that Dr. McGinn has suggested, with one modification. The peripheral edema decreased with therapy, and the week before he died he was almost free from edema, which shows again that cardiac patients now die from infection and infarction rather than from dropsy. That observation has been made before and makes one question just how much good is accomplished by strenuous diuretic therapy, except from an esthetic standpoint. I also brought up the question as to whether the pericardial rub was uremic in origin. I said that it might be, only because of the rise in the nonprotein nitrogen. As Dr. McGinn has said, one of the things that make cardiac patients fail and resist all therapy is multiple pulmonary infarction, which I thought was present in this case.

Clinical Diagnoses

Coronary heart disease.
Pulmonary embolism.

Dr. McGinn's Diagnoses

Hypertensive arteriosclerotic heart disease.
Coronary occlusion, old, right, with posterior myocardial infarction.
Cardiac hypertrophy and dilatation.
Congestive failure, right-sided and left-sided.
Pulmonary infarction, multiple.
Bronchopneumonia (terminal).

Anatomical Diagnoses

Cardiac infarction, healed.
Cardiac aneurysm.
Mural thrombus, left ventricle.
Arteriosclerosis, marked, aortic and coronary.
Pulmonary infarction, multiple, bilateral.
Thrombosis, deep veins of left lower extremity.
Hydrothorax, bilateral.
Hydropericardium.
Peripheral edema.

Pathological Discussion

Dr. Benjamin Castleman: This is a postmortem roentgenogram showing the large number of pulmonary infarcts that this patient had. There were seven in all. One of the infarcts in the left lower lobe was adherent to the pericardium, and I believe that the friction rub was produced by the resultant pleuropericarditis. The deep veins of the left leg were the source of the emboli. There were 750 cc. of straw-colored slightly hemorrhagic fluid in each pleural cavity, 200 cc. in the pericardium and moderate edema of the legs — definite evidence of heart failure. The heart weighed 615 gm. and before opening showed an aneurysm of the left ventricular wall, undoubtedly the site of the infarct that he had had five years before entry. When the heart was opened, the wall of the aneurysm was quite thin, gray-white and fibrous, and involved the apex and the lower half of the interventricular septum. Superimposed on its endocardial surface was an old laminated mural thrombus, 2 to 3 cm. in diameter. There was no evidence of recent infarction. All the coronary arteries were markedly sclerotic and calcified, the lumens being about one fifth of the normal caliber. There was no fresh occlusion. The kidneys weighed 500 gm. and showed practically no vascular disease, an unusual finding in a man of sixty-two.

Dr. Sprague: A pleuropericardial friction rub is not uncommon in patients with pulmonary infarct, and we have found it a helpful point in confirming the diagnosis of deep infarcts with the pleural reaction at the mediastinal surface.

CASE 26422

Presentation of Case

A seventy-three-year-old retired postman entered the hospital complaining of abdominal pain and diarrhea of ten days' duration.

Because of the patient's disorientation, the history was obtained from his son. Three years before admission the patient had suffered from an attack of chest pain and prostration. This attack was not associated with cough or dyspnea, nor had his ankles ever become swollen. Three similar attacks had occurred during the next three years, and his physician had kept him constantly digitalized. Ten days before entry he suddenly became disorientated, fell to the floor and lost motor co-ordination. He was put in a chair and sat there all day, unable to speak plainly or to hold a teacup. Motor co-ordination improved in twenty-four hours, and speech and rationality returned, although his memory seemed to have suffered appreciably. During the next week his muscular co-ordination and mental faculties showed still further improvement. Four days before admission he had abdominal pains, diarrhea and a temperature of 102°F. The abdomen became very tender, but was not distended. The stools were black, but contained no gross blood. The next day the temperature returned to normal, but the diarrhea continued. The day before entry the temperature was 101.5°F., and he went to stool frequently, but passed nothing.

In the past the patient had had scarlet fever complicated by mastoiditis that had resulted in deafness of the right ear. He was said to have been paralyzed in the right side for an unstated period, and his speech had become seriously impaired after a "shock" one year before entry.

Physical examination showed that the patient was undernourished, pale and acutely ill. Numerous areas of senile keratosis were present on the arms and hands. The mouth was dry, and the tongue coated. The heart did not appear to be enlarged. There were no murmurs, but there was complete arrhythmia; the sounds were of poor quality. The apex rate was 168, and the radial pulse 144, with a pulsus alternans. The blood pressure was 154 systolic, 76 diastolic. Resonance and breath sounds were diminished on the left, and a peculiar type of cogwheel tubular respiration was heard over the left second and third interspaces. There was generalized abdominal tenderness, but no masses could be felt.

The temperature was 103.6°F., and the respirations 35.

Examination of the urine showed a ++ test for albumin. Examination of the blood showed a red-cell count of 5,030,000 with a hemoglobin of 17.2 gm. (photoelectric-cell technic), and a white-cell count of 26,700. The nonprotein nitrogen of the blood serum was 35 mg. per 100 cc., and the carbon-dioxide combining power 24.6 vol. per cent. A blood Hinton test and a blood culture were negative. The sputum contained Type 9 pneumococci. Examination of the stools was negative on two occasions.

X-ray films of the chest, taken with a portable machine, were negative. Similar films of the abdomen showed no dilatation of the small bowel or colon; several gas-filled loops of bowel were present in the pelvis. There were no abnormal soft-tissue masses.

On the second hospital day the patient's abdomen was somewhat distended, and there were deep tenderness and slight muscular spasm in the right lower quadrant. Peristalsis appeared to be increased. Rectal examination at this time revealed a mass above the prostate, which was firm, tender and more pronounced on the left side. A steadily rising white-cell count had reached 39,700. He was treated expectantly, and eight days later the mass was larger and equally distributed on both sides. One examiner noted the presence of blood and mucus on the rectal glove, but an examination of the stools, recorded two days later, was negative. The white-cell count rose to 47,700. The patient began to go downhill, becoming weaker and unable to retain fluids by mouth. The cough increased in severity, and rales were heard at the left lung base. On the fifteenth hospital day the mass palpated by rectum had reached even greater proportions, and the center seemed somewhat softened. The patient's condition was considered too critical to attempt surgery, and he died three weeks after admission.

Differential Diagnosis

Dr. Richard H. Wallace: We have an old, disorientated man whose history, obtained from his son, included four attacks of chest pain and prostration during the previous three years. In addition, a year earlier he had had a "shock," with right hemiplegia, which apparently disappeared, and ten days before admission another vascular accident of some sort from which he partially recovered.

On admission he had a rapid, weak pulse with complete arrhythmia, so that there was not much question that he had severe cardiovascular disease. This complicates the picture somewhat. In addition, he had a productive cough, rapid respirations and increasing signs in the chest. Our problem is to try to diagnose the lesion in the abdo-

men. Could the abdominal symptoms be related to the cardiovascular disease? Could they be explained on the basis of embolus, mesenteric thrombosis or dissecting aneurysm of the aorta? I do not believe that any of these fit into the picture.

May we see the x-ray films?

DR. JAMES R. LINGLEY: All we have are films taken with a portable machine. Those of the chest show surprisingly little, in view of the physical findings. Both lung fields appear to be clear. The aorta is tortuous. I cannot tell a great deal about the heart. Certainly it is not tremendously enlarged. This film of the abdomen shows a lot of opaque material in the colon, probably bismuth. There are no dilated loops of colon, and the gas-filled loops that are referred to in the record can be either small bowel or sigmoid; in either case they are not dilated. The film is not sufficiently clear to demonstrate the mass that was noted. There is no x-ray evidence of intestinal obstruction.

DR. WALLACE: With a disorientated patient like this, the history given by the son is perhaps not complete, and it is quite likely that the onset of the abdominal lesion may have been earlier than the record indicates. In fact, it may have occurred at any time during the ten-day period following the last vascular accident. The abdominal pain, diarrhea and temperature of 102°F. suggest some sort of colitis. Acute fulminating ulcerative colitis certainly should give blood and mucus, which he did not have. The history of black stools before admission was not confirmed later, and three examinations of stools showed no blood. On admission the patient merely had general abdominal tenderness. The following day, rectal examination showed a mass above the prostate that increased in size, was tender and subsequently showed softening in the center. The white-cell count was quite high on admission and increased rapidly to 47,000. This is suggestive of some vascular impairment. The other laboratory findings are not helpful. There was no anemia. In fact the red-cell count, hemoglobin and nonprotein nitrogen were a little high. That is probably explainable on the basis of dehydration. With the general story and findings, I believe that the patient had an abdominal infection that localized in the pelvis, and with the onset of the localization, irritation of the bowel and diarrhea. If this is true, we must decide what organ had perforated.

I suspect, as I said before, that the onset was not four days before admission, when he was having diarrhea and a temperature of 102°F., but several days before. If that is so, it is difficult to get a very clear idea of the origin of the perforation. It might conceivably have been a peptic ulcer, but that is extremely unlikely with no previous history of indigestion or pain in a man of this age. He might have had a perforated diverticulum of the sigmoid, with localization of an abscess. Perforation of carcinoma of the colon is a possibility, but the absence of earlier symptoms and the absence of blood in the stools in the hospital make that unlikely. While in the hospital, one observer noted tenderness and spasm in the right lower quadrant, even though the mass was considered as being more prominent in the left side of the pelvis. It was subsequently noted that it was as large on the right as on the left. I must come to the conclusion that this was a perforation of some sort, with localization in the pelvis; it might possibly be complicated by the secondary involvement of the small intestine, and some interference with the blood supply might account for the high white-cell count. The latter may also have been influenced by the increasing infection in the chest. The best diagnosis that I can make under the circumstances is acute appendicitis, with rupture and an abscess localizing in the pelvis.

DR. WILLIAM B. BREED: Those of us who watch these patients before death obtain a more complete picture than that given in an abstract. This man was very old and was disorientated since the previous cerebral episode; it was perfectly obvious that the less one did to him the better. We hoped that he might be able to get through his sickness without surgery. Because of the irregularity of the heart, the previous cerebral episode and the abdominal pain with high white-cell count, we, like Dr. Wallace, considered mesenteric thrombosis. On the other hand, as time went on that diagnosis became less probable, and the choice was between acute appendicitis with perforation and rupture of a diverticulum. The discharge diagnosis was pelvic abscess, diverticulitis, auricular fibrillation and arteriosclerotic heart disease. The indurated abscess felt by rectum began to soften, and although there was some thought of draining it from below, nothing was finally attempted.

DR. MARSHALL K. BARTLETT: I saw the patient the day after he was admitted, and because the signs in the right lower quadrant were quite definite I thought that he probably had appendicitis, with perforation and abscess. These signs disappeared, and abdominal examination showed nothing but a little tenderness on the left side. The rectal findings became more evident, and a diagnosis of diverticulitis with abscess seemed more probable than a diagnosis of appendicitis.

Clinical Diagnoses

Appendiceal abscess?
Diverticulitis?
Coronary heart disease.
Bronchopneumonia.

Dr. Wallace's Diagnosis

Acute appendicitis, with rupture and pelvic abscess.

Anatomical Diagnoses

Diverticulitis of the sigmoid, with perforation.
Retroperitoneal abscess.
Bronchopneumonia.
Cardiac hypertrophy, hypertensive type.
Arteriosclerosis, marked, coronary, aortic and renal.

Pathological Discussion

Dr. Tracy B. Mallory: The postmortem examination showed no peritonitis but a very well localized retroperitoneal abscess that lay against the sigmoid. The entire sigmoid showed numerous diverticulums, one of which was inflamed and perforated and was evidently the cause of the abscess. Despite the very high white-cell count, there was no evidence of interference with circulation. All the loops of bowel were of normal color. The heart, as might be expected, was slightly hypertrophied and showed considerable coronary disease without, however, any scars or any points of complete occlusion of the coronaries. There was a terminal, very extensive bronchopneumonia.

Dr. Maurice Fremont-Smith: I should like to criticize the use in the record of the phrase "pulsus alternans"; this has no meaning in the presence of complete cardiac irregularity. Perhaps they meant that the patient had a pulse deficit or perhaps it was a bigeminal pulse due to extrasystoles.

The New England
Journal of Medicine

Formerly the
Boston Medical and Surgical Journal
Established in 1828

Owned by the Massachusetts Medical Society and Published under the Jurisdiction of the Committee on Publications

Official Organ of
The Massachusetts Medical Society
The New Hampshire Medical Society
The Vermont State Medical Society

Editorial Board

Joseph Garland, M.D. — John P. Sutherland, M.D.
William B. Breed, M.D. — Stephen Rushmore, M.D.
George R. Minot, M.D. — Henry R. Viets, M.D.
Frank H. Lahey, M.D. — Robert M. Green, M.D.
Shields Warren, M.D. — Charles C. Lund, M.D.
George L. Tobey, Jr., M.D. — John F. Fulton, M.D.
C. Guy Lane, M.D. — A. Warren Stearns, M.D.
William A. Rogers, M.D. — Dwight O'Hara, M.D.

Associate Editors

Thomas H. Lanman, M.D. — Donald Munro, M.D.
Henry Jackson, Jr., M.D.
Walter P. Bowers, M.D., Editor Emeritus
Robert N. Nye, M.D., Managing Editor
Clara D. Davies, Assistant Editor

Subscription Terms: $6.00 per year in advance, postage paid, for the United States; Canada, $7.04 per year; $8.52 per year for all foreign countries belonging to the Postal Union.

Material for early publication should be received not later than noon on Saturday.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston, Massachusetts.

CO-ORDINATING MEDICAL-PREPAREDNESS COMMITTEE

Official action has finally been taken whereby a co-ordinating committee for medical preparedness has been appointed. This committee, known as the Health and Medical Committee, is a subordinate body to the Council of National Defense, and is composed of the following: Dr. Irvin Abell, of Louisville, Kentucky, chairman; Dr. Lewis H. Weed, of Baltimore; Surgeon General Magee, United States Army; Surgeon General McIntire, United States Navy; and Surgeon General Parran, United States Public Health Service. Since Dr. Abell is chairman of the Committee on Medical Preparedness of the American Medical Association, and Dr. Weed, chairman of the Division of Medical Sciences of the National Research Council, it is difficult to conceive how a better selection of personnel could have been made. The committee is empowered to appoint various subcommittees to furnish information and advice in regard to special problems, and many of these subcommittees are already functioning.

The committee is specifically authorized "to advise the Council of National Defense regarding the health and medical aspects of national defense and to co-ordinate health and medical activities affecting national defense." In exercising this authority it may request the aid of the laboratory, equipment and advice of the medical departments of the Army, Navy and Public Health Service, and may enter into contracts with and transfer available funds to these departments, as well as with or to individuals or educational and scientific institutions, for studies, investigations and reports.

The appointment of a co-ordinating committee rather than a co-ordinator appears to have been a wise move, for, as pointed out in the August 8 issue of the *Journal*, "the responsibilities [of medical preparedness] seem to be too varied and too great to be shouldered by any one individual." With the committee constituted as it is, the medical profession and the country at large can be assured that the problems of medical preparedness will be handled wisely and expediently.

SALVATION ARMY APPEAL

As in previous years, a group of public-spirited men and women of the business world are leading the Greater Boston Annual Maintenance Appeal of the Salvation Army. The drive, which began on October 7 with a dinner at the Boston City Club, will last until November 9.

The campaign organizations in the corps cities of Cambridge, Chelsea, Everett, Malden, Medford and Somerville will raise $25,000 of the $200,000 that represents the Salvation Army's goal for 1940–1941. A quota of $38,000 will be assigned to the thirty-one towns of Greater Boston where no corps organizations exist.

The amount to be collected is an increase of $5000 over the quota set last year. The money will pay for the maintenance of more than thirty institutions that serve the needy.

This is indeed an appeal, a request for support

of an organization that has done such splendid and unselfish work among the less fortunate members of the community. Because physicians in particular recognize the value of the Salvation Army's services, they will undoubtedly be the first to respond.

MEDICAL EPONYM

Eck's Fistula

Nikolai Vladimirovich Eck (b. 1849) of St. Petersburg (now Leningrad), published a "preliminary communication" in the *Voyenno-Meditsinsky Jurnal* (130:1, 1877) entitled "K voprosu o perevyazkie vorotuoi veni [Ligature of the Portal Vein]." A portion of the translation follows:

> If in the dog, after establishing a free communication between the inferior vena cava and the portal vein, one ties off the portal vein, the change in direction of the blood flow and the deprivation of the liver of blood from the portal vein produce no serious results in the organism. The animal recovers from the operation, his nutrition improves after recovery, and he remains in perfect condition.

The technic of the operation is described and its possible application to the treatment of human ascites mentioned.

The medium by which this experimental procedure attained its first wide publicity was an article entitled "Die Eck'sche Fistel zwischen der unteren Hohlvene und der Pfortader und ihre Folgen für den Organismus [Eck's Fistula between the Inferior Vena Cava and the Portal Vein and Its Results upon the Organism]" by Hahn, Massen, Nencki and Pavlov, which appeared in the *Archiv für Experimentelle Pathologie und Pharmakologie* (32:161–210, 1893).

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

Raymond S. Titus, M.D., *Secretary*
330 Dartmouth Street
Boston

The Maternal Mortality Study In Massachusetts for 1939

This is the third year that the Section of Obstetrics and Gynecology of the Massachusetts Medical Society has carried on an investigation of maternal mortality. It is to be continued through 1941. Two hundred and fifty-five cases were reviewed during 1939, and of these, 2 were found to be nonpuerperal, giving a total of 253 puerperal deaths. The maternal death rate for 1939, 3.4 per cent per 1000 live births, as given by the Massachusetts Department of Public Health, is very encouraging when compared with the rates for 1937 and 1938, which were 4.1 and 3.7 per cent respectively. A comparative analysis of the puerperal causes of death for the past three years is as follows:

Cause of Death	No. of Deaths		
	1937	1938	1939
Sepsis (including septic abortions)	111	66	74
Medical deaths (pneumonia, cardiac disease, chronic nephritis and so forth)	57	54	57
Embolus	32	28	23
Hemorrhage (including separated placenta and placenta previa)	30	36	36
Albuminuria and eclampsia	29	31	32
Accidents of labor	13	6	8
Abortions (not septic)	9	3	4
Surgical deaths	10	13	5
Anesthesia	6	9	4
Ectopic pregnancy	6	12	5
Transfusion	3	2	3
Shock	3	7	2
Pernicious vomiting	4	5	
Sudden death	2		
Dystocia, with acute dilatation of heart		1	
Suicide		2	
Mesenteric thrombosis		1	
Totals	315	276	253

Sixty-seven autopsies were obtained in 1939, a percentage of 23; this is an improvement, but an even greater number should be performed.

Sepsis was still the greatest cause of mortality, with 74 attributable deaths. Of these there were 27 septic abortions, which might have been helped by chemotherapy. Either chemotherapy was not considered or it was considered too late to be of any appreciable value. It is too much to hope that chemotherapy as we know it today can be of any curative value in peritonitis.

It is gratifying that the number of cases of pernicious vomiting has fallen, no cases having been reported. This means better earlier diagnosis and treatment, hence better obstetrics.

It is lamentable that cardiac disease has claimed 16 lives. These patients should never have been allowed to become pregnant; and if pregnant, they should have been aborted. The same may be said of the single patient who died of chronic nephritis.

Toxemias, with and without eclampsia, still take much too large a toll. Until obstetrics is more intelligently practiced, this number cannot be decreased. There will always be a few ignorant patients who do not present themselves for care until the disease is beyond help. Such deaths are not the fault of the medical profession.

Anesthetic deaths should be prevented; there were 4 in 1939. The 3 transfusion deaths are also

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

evidence of imperfect study and should be prevented.

Although the 1938 death rate from cesarean section per se is only 2.7, a more intelligent decision as to whether the operation is or is not necessary would reduce the number of cesareans done and would consequently lower the mortality from this cause.

It has come to the attention of the committee that some hospitals in Massachusetts are not following the *International List of Causes of Death* in making up their yearly reports. This list is followed at the State House, and should be used by every hospital in order that their yearly reports, based on the same criteria, may furnish accurate statistics. According to the *International List of Causes of Death,* every pneumonia occurring in pregnancy is classified as a maternal death, as is every cardiac death occurring during pregnancy. If this list were followed in all hospitals, their mortality rates would be honestly comparable.

The officers of the section are again grateful for the co-operation of the physicians in Massachusetts, and ask for their further support until this study has been completed.

DEATHS

DAVIS — Frank A. Davis, M.D., of Hampton, New Hampshire, formerly of Boston, died October 8. He was in his seventy-fifth year.

He attended the University of New Hampshire and received his degree from Boston University School of Medicine in 1898. For nineteen years he practiced medicine in Boston. He was surgeon in the X-ray Department of the Boston Dispensary in 1905; in 1913 he was appointed physician-in-charge.

Dr. Davis received an honorary Sc.D. degree from the University of New Hampshire in 1913. In 1917 he enlisted in the Medical Corps of the United States Army and was later associated with the Veterans' Bureau in Washington and New York City. At the time of his retirement in 1929, he was in charge of the bureau's physiotherapy department in the Bronx, New York City.

He was a member of the Massachusetts Medical Society and the American Medical Association.

His widow and three nephews survive him.

ENEBUSKE — Claës J. Enebuske, M.D., of Lund, Sweden, formerly of Cambridge, Massachusetts, died July 4. He was in his eighty-sixth year.

Dr. Enebuske received his degree from Harvard Medical School in 1896. He was a member of the Massachusetts Medical Society and the American Medical Association.

LEONARD — William J. Leonard, M.D., of Provincetown, died July 25. He was in his seventy-first year.

Dr. Leonard received his degree from the College of Physicians and Surgeons of Baltimore in 1896. He was formerly police-department surgeon and city physician of Springfield. At one time he was on the staffs of the Mercy Hospital and the City of Springfield Infirmary, Springfield.

Dr. Leonard was a former member of the Massachusetts Medical Society and the American Medical Association.

SWAN — Roscoe W. Swan, M.D., of Worcester, died October 13. He was in his eighty-first year.

Born in Framingham, he attended Chauncy Hall School, Massachusetts State College and Boston University and received his degree from Harvard Medical School in 1882. Dr. Swan practiced for eight years in Worcester and then studied in Europe for fourteen years, returning to Worcester in 1904 to specialize in intestinal diseases.

He was a member of the Massachusetts Medical Society and the American Medical Association and was also medical director of the Massachusetts Protective Association.

His widow survives him.

MISCELLANY

RÉSUMÉ OF COMMUNICABLE DISEASES IN MASSACHUSETTS FOR AUGUST, 1940

Diseases	August 1940	August 1939	Five-Year Average*
Anterior poliomyelitis	9	15	130
Chicken pox	81	120	108
Diphtheria	12	13	16
Dog bite	1206	1153	1102
Dysentery, bacillary	15	12	11
German measles	20	14	42
Gonorrhea	366	432	493
Lobar pneumonia	93	77	117
Measles	507	281	201
Meningococcus meningitis	3	2	5
Mumps	157	83	151
Paratyphoid B fever	36	3	10
Scarlet fever	78	82	129
Syphilis	297	367	445
Tuberculosis, pulmonary	319	317	305
Tuberculosis, other forms	28	27	33
Typhoid fever	12	10	12
Undulant fever	1	0	4
Whooping cough	509	429	468

*Based on figures for preceding five years.

Rare Diseases

Anterior poliomyelitis was reported from: Braintree, 1; Chicopee, 1; Holyoke, 2; Lynnfield, 1; Millbury, 1; Stockbridge, 1; Worcester, 2; total, 9.

Anthrax was reported from: Lynn, 1; total, 1.

Diphtheria was reported from: Adams, 1; Boston, 1; Canton, 1; Chelsea, 1; Framingham, 4; Leverett, 1; Somerville, 2; Wrentham, 1; total, 12.

Dysentery, bacillary, was reported from: Chicopee, 1; Danvers, 3; Lawrence, 1; Lowell, 4; Quincy, 1; Worcester, 5; total, 15.

Infectious encephalitis was reported from: Holyoke, 1; total, 1.

Meningococcus meningitis was reported from: Cambridge, 1; Hull, 1; Millbury, 1; total, 3.

Paratyphoid B fever was reported from: Beverly, 1; Cambridge, 1; Fall River, 1; Haverhill, 1; Lowell, 1; Lynn, 1; Somerville, 1; Tewksbury, 29; total, 36.

Pellagra was reported from: Boston, 1; total, 1.

Pfeiffer bacillary meningitis was reported from: Northampton, 1; total, 1.

Septic sore throat was reported from: Boston, 1; Fall River, 1; Saugus, 1; total, 3.

Tetanus was reported from: Fall River, 1; Somerville, 1; Worcester, 1; total, 3.

Trachoma was reported from: Boston, 1; total, 1.

Trichinosis was reported from: Boston, 3; Haverhill, 1; total, 4.

Typhoid fever was reported from: Boston, 3; Holden, 1; Medford, 1; Quincy, 6; Springfield, 1; total, 12.

Undulant fever was reported from: Plymouth, 1; total, 1.

Anterior poliomyelitis continued to show unusually low incidence.

Measles, mumps, pulmonary tuberculosis and whooping cough were reported above the five-year averages.

Scarlet fever was reported at a record low figure both for this and any other month ever recorded.

Diphtheria, lobar pneumonia, tuberculosis (other forms), German measles and chicken pox were reported below the five-year averages.

Meningococcus meningitis and undulant fever showed low incidence.

Typhoid fever was reported at a figure equal to that of the five-year average.

Dog bite was reported at a record high figure.

Animal rabies showed low incidence. An active focus was noted in Hanover.

NOTICES

ANNOUNCEMENTS

Jack Gurwitz, M.D., announces the opening of an office at 434 North Main Street, Randolph.

Aaron Kaufman, M.D., announces the removal of his office from 395 Commonwealth Avenue to 483 Beacon Street, Boston.

Joseph Sklaver, M.D., announces the opening of an office at 111 West Main Street, Waterbury, Connecticut.

PETER BENT BRIGHAM HOSPITAL

A joint medical and surgical clinic at the Peter Bent Brigham Hospital will be held on Wednesday, October 23, from 2 to 4 p.m. Drs. E. C. Cutler and Soma Weiss will speak, their subject being "Abdominal Pain." A clinicopathological conference, conducted by Dr. Elliott C. Cutler, will take place from 4 to 5 p.m.

Physicians and students are cordially invited to attend.

CARNEY HOSPITAL

The monthly clinical meeting and luncheon of the Carney Hospital will be held in Carney Hospital Auditorium on Monday, October 21, at 11:30 a.m.

Program

Business.

Case Report.

Clinicopathological Conference: A case of acute pulmonary tuberculosis or of miliary tuberculosis. Drs. John L. Doherty, Edward J. Leonard and Francis J. Wenzler.

Physicians and medical students are invited to attend.

TRUDEAU SOCIETY OF BOSTON

There will be a meeting of the Trudeau Society of Boston in the auditorium of the Beth Israel Hospital on Thursday evening, October 24, at 8:00. Dr. Richard H. Overholt will speak, his subject being "The Management of Pulmonary Abscess." The discussion will be opened by Drs. Theodore L. Badger and Henry L. Cabitt.

BOSTON LYING-IN HOSPITAL

A meeting of the medical alumni of the Boston Lying-in Hospital will be held at the hospital on October 24. This has been designated as "Walter Channing Day," in commemoration of one of the original founders of the hospital and the first professor of midwifery and medical jurisprudence at Harvard Medical School.

The scientific portion of the program will be held in the amphitheater of Building D, Harvard Medical School, from 11:30 a.m. to 12:30 p.m. and from 2:00 to 4:00 p.m.

HARVARD MEDICAL SOCIETY

The next meeting of the Harvard Medical Society will be held on Tuesday, October 22, in the amphitheater of the Peter Bent Brigham Hospital at 8:15 p.m.

Program

Presentation of Cases.

Endocrine Control of the Reproductive Cycle.

Pituitary-Ovarian Interrelationships of the Estrous Cycle. Dr. F. H. Hisaw.

The Regulation of Corpus Luteum Function. Dr. E. B. Astwood.

BOSTON DOCTORS' SYMPHONY ORCHESTRA

The Boston Doctors' Symphony Orchestra will rehearse under Alexander Thiede, former concertmaster with the Cleveland Symphony Orchestra, every Thursday at 8:30 p.m. Those interested in becoming members should communicate with Dr. Julius Loman, Pelham Hall Hotel, Brookline (BEA 2430).

MASSACHUSETTS GENERAL HOSPITAL

A meeting of the Hospital Research Council will be held in the Ether Dome of the Massachusetts General Hospital on Tuesday, October 29, at 5:00 p.m.

Program

Clinical Aspects and Renal Function. Dr. John H. Talbott.

Constituents of Blood and Respiratory Functions. Drs. D. Bruce Dill and William H. Forbes.

Therapeutic Considerations in Schizophrenia. Dr. Kenneth J. Tillotson.

TAUNTON STATE HOSPITAL

The Taunton State Hospital, Taunton, Massachusetts, announces the extension of its clinic facilities. Beginning the week of October 13, child guidance clinics, where children with their special problems may be studied, and later treated, will be held in the City Hall Annex, Fall River, each Tuesday, and in the Olympia Building, New Bedford, each Wednesday, from 1:00 to 4:00 p.m. by appointment. Mental health clinics for adults will be held in Fall River each Tuesday and in New Bedford each Wednesday, between 9:00 and 11:30 a.m. Those who desire consultation with a psychiatrist will be welcomed, but appointment must be made, as in the past, through a social agency or a physician.

NORFOLK DISTRICT MEDICAL SOCIETY

A stated meeting of the Norfolk District Medical Society will be held at the Hotel Puritan, Boston, on Tuesday evening, October 29, at 8:00 (Tel. KEN 1480).

PROGRAM

Business.
Medical Preparedness. Drs. Thomas R. Goethals, Frederick J. Bailey and Donald E. Currier.
Discussion.
Collation.

MASSACHUSETTS SOCIETY FOR MENTAL HYGIENE

The Massachusetts Society for Mental Hygiene announces that the Northeastern Conference on Mental Health in the Community will be held in Salem at the Hotel Hawthorne and the Lydia E. Pinkham Memorial on Friday, November 15. This will be an all-day conference, with morning, afternoon and evening sessions.

The speaker of the evening will be Dr. Ira S. Wile, formerly commissioner of education, New York City, who will discuss the central theme of the conference — "The Mental Health of the Community."

There will be a special luncheon for physicians at the Hotel Hawthorne at 12:30 p.m. Dr. Harry C. Solomon, associate professor of psychiatry, Harvard Medical School, will speak, his subject being "The Diagnosis and Treatment of Mental Disorders." All physicians, especially those in the northeastern part of the State, are welcome.

This conference has been endorsed and is being sponsored by the Essex South District Medical Society.

SOCIETY FOR RESEARCH IN CHILD DEVELOPMENT

The Society for Research in Child Development is holding its fourth biennial meeting at the Harvard Medical School on November 8 and 9. This is a national organization of scientific workers who are actively studying some phase of the development of children. The membership of this society represents a wide variety of scientific disciplines, and this breadth of interest of the membership is reflected in the program. The latter contains reports of interest to the pediatrician, physiologist, nutritionist, psychologist, dentist and persons in other special fields. The primary purpose of the meetings of this society, however, is to bring together persons with widely divergent experiences and interests, to familiarize those in each field with the advances which have been made in the other fields, and to apply these collective advances to the better understanding of the total development of children.

A fee is charged for registration, which assures accommodation at all the meetings, but students and members of the interested professions will be admitted to individual sessions, without registration, so far as space permits at the time scheduled. The topics and times of the various sessions are as follows:

FRIDAY MORNING, NOVEMBER 8. Harvard Medical School, Amphitheater, Building E.

9:30–11:00 Panel discussion of technical problems involved in longitudinal studies of physical growth.

11:10–12:40 Panel discussion of technical problems involved in longitudinal studies in the psychological area.

11:15–12:45 Dental and nutritional studies being conducted at the Forsyth Dental Infirmary. This session will be held at the Forsyth Dental Infirmary.

FRIDAY AFTERNOON, NOVEMBER 8. Harvard Medical School, Amphitheater, Building C.

2:00–5:00 Symposium on neurological and behavior characteristics of the newborn.

SATURDAY MORNING, NOVEMBER 9. Harvard Medical School, Amphitheater, Building B.

9:00–12:00 Symposium on adolescent development.

SATURDAY AFTERNOON, NOVEMBER 9. Children's Hospital, Amphitheater.

2:00–3:00 Reports of studies of child development from the Center for Research in Child Health and Development, Harvard School of Public Health.

3:30–5:00 Studies of development following injury to the central nervous system in early life.

Those interested in obtaining further details as to the topics covered and the participants in the various sessions listed may obtain the same by communicating with the Department of Child Hygiene, Harvard School of Public Health.

AMERICAN CONFERENCE ON INDUSTRIAL HEALTH

Industrial physicians and manufacturers from all over the country will attend the American Conference on Industrial Health to be held Thursday, November 14, at the Towers Club in Chicago. The conference will be sponsored by the American Association of Industrial Physicians and Surgeons, a 25-year-old organization.

This first meeting of the American Conference on Industrial Health has for its purpose the correlation of viewpoints of all persons who are interested in promoting industrial health. These include employers, physicians, industrial hygienists, labor organizations, psychiatrists, insurance companies, public relations men, safety experts and the legal profession.

Dr. Clarence O. Sappington, of Chicago, co-chairman of the committee with Dr. Edward C. Holmblad, stated: "We have invited the manufacturer and other persons to attend and participate in the convention so that we may prove the practical value and application of industrial health work, and so that they may realize how much time and money may be saved yearly by such measures."

Among the prominent speakers who will talk at the convention sessions are: Dr. Morris Fishbein, editor of the *Journal of the American Medical Association;* Mr. B. C. Heacock, president of the Caterpillar Tractor Company; Dr. Volney S. Cheney, medical director of Armour and Company; and Mr. J. M. Conway, representing the National Association of Manufacturers, New York City.

The conference, which is scheduled to begin at 9:30 a.m., will conclude with a dinner session, at which Dr. Fishbein and Mr. Conway will speak.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING SUNDAY, OCTOBER 20

SUNDAY, OCTOBER 20

*7 p.m. Medical Horizons. Dr. Nathan B. Van Etten. St. Paul's Cathedral, Boston.

MONDAY, OCTOBER 21

*11:30 a.m. Carney Hospital, monthly clinical meeting and luncheon.

12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital amphitheater.

TUESDAY, OCTOBER 22

*9–10 a.m. Simple X-Ray of the Skull as an Aid to Neurological Diagnosis. Dr. Kurt Goldstein. Joseph H. Pratt Diagnostic Hospital.

12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital amphitheater.

8:15 p.m. Harvard Medical Society. Amphitheater, Peter Bent Brigham Hospital. Page 647.

WEDNESDAY, OCTOBER 23

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12 m. Clinicopathological conference. Children's Hospital.

*2–4 p.m. Abdominal Pain. Drs. E. C. Cutler and Soma Weiss. Joint medical and surgical clinic. Peter Bent Brigham Hospital.

THURSDAY, OCTOBER 24

*9–10 a.m. Hemorrhagic Diathesis. Dr. Eugene Lozner. Joseph H. Pratt Diagnostic Hospital.

11:30 a.m.–12:30 p.m. and 2–4 p.m. "Walter Channing Day." Boston Lying-in Hospital.

8 p.m. The Management of Pulmonary Abscess. Dr. Richard H. Overholt. Trudeau Society of Boston. Auditorium, Beth Israel Hospital.

FRIDAY, OCTOBER 25

*9–10 a.m. Clinicopathological conference. Dr. Fuller Albright and Dr. H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.

8:15 p.m. Massachusetts Memorial Hospitals, staff meeting.

SATURDAY, OCTOBER 26

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*Open to the medical profession.

OCTOBER 14–25 — 1940 Graduate Fortnight of the New York Academy of Medicine. Page 305, issue of August 22.

OCTOBER 21 — American Board of Internal Medicine. Page 369, issue of February 29.

OCTOBER 29 — Massachusetts General Hospital. Hospital Research Council. Page 647.

NOVEMBER 8, 9 — Society for Research in Child Development. Page 648.

NOVEMBER 13, 14 — New England Postgraduate Assembly. Cambridge, Massachusetts.

NOVEMBER 14 — Pentucket Association of Physicians. Page 263, issue of August 15.

NOVEMBER 14 — American Conference on Industrial Health. Page 648.

NOVEMBER 15 — Massachusetts Society for Mental Hygiene. Page 648.

DECEMBER 27–29 — National Convention of the Association of Medical Students, Boston.

JANUARY 4, 1941 — American Board of Obstetrics and Gynecology. Page 1064, issue of June 20.

MARCH 8 — American Board of Ophthalmology. Page 201, issue of August 1.

APRIL 21–25 — American College of Physicians. Page 1065, issue of June 20.

MAY 21, 22 — Massachusetts Medical Society, Boston.

JUNE 2–6 — American Medical Association. Cleveland, Ohio.

DISTRICT MEDICAL SOCIETIES

NORFOLK

OCTOBER 29 — Page 648.

SUFFOLK

OCTOBER 30 — Page 604, issue of October 10.

NOVEMBER 7 — Censors' meeting. Page 305, issue of August 22.

JANUARY 29 — Page 604, issue of October 10.

APRIL 30 — Page 604, issue of October 10.

WORCESTER

NOVEMBER 13 — Grafton State Hospital, Grafton.

DECEMBER 11 — St. Vincent Hospital, Worcester.

JANUARY 8, 1941 — Worcester City Hospital, Worcester.

FEBRUARY 12 — Worcester State Hospital, Worcester.

MARCH 12 — Memorial Hospital, Worcester.

APRIL 9 — Hahnemann Hospital, Worcester.

Supper will be served at 6:30 p.m. followed by a business meeting and scientific program.

BOOK REVIEWS

Principles of Orthopedic Surgery. By James Warren Sever, M.D. Third edition. 8°, cloth, 418 pp., with 220 illustrations. New York: Macmillan Company, 1940. $3.25.

The third edition of this textbook by a well-known representative of the "Boston School of Orthopaedic Surgery" shows an admirable attempt to bring the book up to date. It is written in a clear, concise manner. The suggestions for treatment and the conclusions are practical. The care of the patient, particularly the nursing care, is treated adequately. The content of any textbook is dependent largely on the experience of the author; thus, in this treatise, juvenile diseases and deformities are discussed at length, but the orthopedic disabilities of adults are only briefly mentioned. Tuberculosis of the bones and joints is probably given more attention than the disease merits at the present time. The excellent chapter on the use of apparatus would probably be improved by a few line drawings of the braces that are discussed. For doctors and medical students the work can be recommended as a supplementary textbook. For the teaching of nurses, physiotherapeutists and others who aid physicians in the care of orthopedic disabilities it can be recommended unreservedly.

Carbohydrate Metabolism: Four papers presented in a symposium held at the meeting of the American Physiological Society at Toronto, Canada, April 29, 1939. Reprinted from *Endocrinology*, **26**:285-351, 1940. By various authors. 4°, paper, 67 pp., with 6 charts and 14 tables. Menosha, Wisconsin: George Banta Publishing Company, 1940. $1.00.

Four papers, presented in a symposium on carbohydrate metabolism at the Toronto meeting of the American Physiological Society in April, 1939, have been reprinted in pamphlet form from *Endocrinology*. It would be difficult to find a more outstanding group of workers in this field than are here represented. The chairman of the symposium was Professor C. H. Best, and those participating included C. F. Cori, Samuel Soskin, C. N. H. Long, and F. G. Young, of London, England.

In the first paper Cori discusses glycogen breakdown and synthesis in animal tissues. No one is better qualified to speak of glycogen than is this investigator, who has participated in much of the best recent research work concerning it. He emphasizes the fundamental importance of the enzymes which are concerned in the degradation and synthesis of glycogen. It is on them that changes in liver and muscle glycogen depend, and through them that insulin, epinephrine, and other hormones act.

Soskin's contribution is entitled "The Liver and Carbohydrate Metabolism." He presents some of the newer evidence which invalidates the orthodox interpretations of the D:N ratio, the R.Q. and the production of ketone bodies. He reviews some of the recent work showing that glycogen is formed from fatty acids in the liver and that the completely diabetic organism does utilize sugar to a certain extent. He shows that the regulation of the blood-sugar level lies primarily in the liver and its glycogen mechanism, not in the pancreas and insulin production.

The adrenal cortex and carbohydrate metabolism are dealt with by Long, Katzin and Fry, of the Department of Physiological Chemistry, Yale University. In carefully controlled experiments with rats and mice they show that the adrenocortical hormone has a direct, positive action on carbohydrate and protein metabolism, causing a marked rise in liver glycogen and blood sugar at the expense of increased protein catabolism, in both normal and adrenalectomized animals. The hormone also has a diabetogenic effect in hypophysectomized, partially depancreatized rats, which is synergistic with that of anterior pituitary extract.

Young, in a brief paper on the pituitary gland and carbohydrate metabolism, discusses a number of different

effects of anterior pituitary extracts which may be concerned in the production of diabetes in normal animals by the injection of such extracts. He distinguishes an insulin-insensitivity effect, which may occur without any rise in the blood-sugar level; a ketogenic effect, which may result through diminished catabolism of carbohydrate and protein; a diabetogenic effect, including glycosuria in normal animals and possibly due to a diminished rate of insulin secretion by the pancreatic islets; and a pancreotropic effect, involving hyperplasia of islet tissue. There is evidence that the diabetogenic factor may be related to, or even contained in, the growth hormone.

This symposium affords an excellent review of significant recent work in carbohydrate metabolism.

Modern Medical Therapy in General Practice. Vol. 1, 2 and 3. Edited by David Preswick Barr, A.B., M.D., LL.D., Busch Professor of Medicine, Washington University; and physician-in-chief, Barnes Hospital, St. Louis. 4°, cloth: Vol. 1, 1230 pp., with 111 tables, 65 figures and 3 plates; Vol. 2, 1282 pp., with 42 tables, 20 figures and 5 charts; Vol. 3, 1215 pp., with 19 tables and 43 figures. Baltimore: Williams & Wilkins Company, 1940. $35.00.

In three enormous volumes, weighing over 16 pounds, the whole subject of modern medical therapy is considered under the direction of Dr. David P. Barr, physician-in-chief to the Barnes Hospital, St. Louis, and professor of medicine, Washington University.

The vast undertaking is the result of a co-operative endeavor by many of the outstanding physicians of America. Each subject is considered in detail by a specialist in the field, and all the papers are brought together under careful editorship. The work is divided into sections on general diseases, infectious diseases, diseases of the nervous system, diseases of the gastrointestinal tract and diseases of the other organs and systems. The volumes, therefore, cover the whole field of medicine, including specialized parts, such as the skin, the ear and the eye. Surgical treatment is occasionally mentioned, but the entire work is devoted almost exclusively to medical treatment.

Like any work of this type, there is marked variation in the value of the chapters. Some are carefully written by men obviously well qualified; others are of less value. One of the best sections of the book is that contributed by Dr. Barr on the use of drugs in relation to general therapy. There are excellent articles, however, by other men, details of which cannot be given in a brief review. In general, these volumes have set a high standard, and the work can be recommended. In many chapters, there are references to the literature, although there seems to be no uniformity in regard to this important aspect of medical literature. A few mistakes, moreover, have crept into the bibliographies.

It should be pointed out that all material in a book of this type cannot be accepted as the best form of treatment for any individual patient. For example, physicians specializing in such subjects as electrotherapy, physiotherapy and occupational therapy are likely to overemphasize the importance of their particular field of endeavor. This is certainly true in this book, and unfortunately the editor has not seen fit to curtail a certain amount of overenthusiasm expressed in some of the articles.

One unusual feature of the book is the relative lightness of the enormous volumes. They are, however, too large, and the work would have been much more useful had it been divided into six or eight volumes rather than three. There are a few illustrations, which do not add much to the value of the text.

International Medical Annual: A year book of treatment and practitioner's index. Edited by H. Letheby Tidy, M.A., M.D. (Oxon.), F.R.C.P., and A. Rendle Short, M.D., B.S., B.Sc., F.R.C.S. 8°, cloth, 545 pp., with 65 plates. Baltimore: Williams & Wilkins Company, 1940. $6.00.

This sound digest of medical thought continues, after fifty-eight years of existence, to be the leading publication of its kind in the field. Written by British physicians of outstanding merit, the articles, carefully documented and illustrated, are brief essays on the latest developments in medicine. In arrangement and size the volume does not differ from its predecessors. It is difficult to think of any physician, whatever his particular field of interest, who would not profit by a thoughtful perusal of this volume.

L'Examen du Malade. By P. Delmas, G. Giraud, E. Jeanbrau, E. Leenhardt, J. Margarot, P. Pages, V. Riche, L. Rimbaud, J. Terracol and H. Villard, professors of the Faculty of Medicine of Montpellier. 12°, paper, 365 pp. Paris: Masson et Cie, 1939. 45 Fr. fr.

The second edition of this book shows considerable improvement over the first issue by introducing diagnosis in the field of psychiatry and endocrinology. On the whole, it is an excellent summary of most of the common present-day diagnostic methods. Short and to the point, it can be considered a review book of merit.

Studies in the Development of Young Children. By Nancy Bayley. 8°, paper, 45 pp., Berkeley University of California Press, 1940. 35 cents.

This pamphlet embraces studies of 61 Berkeley children, 30 girls and 31 boys, during the first decade of life. Growth and development in body, mind and personality are considered, plus the influence of disease and other factors in the environment. The discussions are, however, of the briefest, and as they stand, give rise to no new conclusions. They need amplification or extension, or both, to be of value.

Mammalian Genetics. By William E. Castle, Ph.D., Sc.D. 8°, cloth, 169 pp., with 131 illustrations and 8 tables. Cambridge: Harvard University Press, 1940. $2.00.

No author could be better qualified than Dr. Castle to write an introduction to mammalian genetics. This volume should make a strong appeal to students in colleges, particularly when it is used in conjunction with the laboratory guide prepared by the same author. The illustrations are clear cut. There are references at the end of each of the nineteen chapters. A discussion of the heredity of man is not included in this book because heredity has to be investigated by methods other than those of experiment.

Dr. Castle shows that the general features of organization are probably dependent on the general features of organization of the living substance in each group and that the details of organization are inherited in accordance with Mendel's law. He points out that the uniting gametes although not different morphologically may yet vary physiologically. In the chapter on sex determination, consideration is given to the operation of three different agencies: chromosomal, environmental and endocrine. It is significant to note that the author thinks it illogical to ascribe action either to nuclear activity alone or to plasmatic activity alone; the two acting together should be considered. This book will no doubt be on the shelves in every biological library and laboratory.